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PROLONGED TREATMENT OF EXOPHTHALMIC GOITER BY IODINE ALONE*

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The value of a short intensive course of iodine medication as a method of preparing a patient with exophthalmic goiter for thyroidectomy has been unquestioned since the report of Plummer [1] in 1923. Following his announcement, the use of iodine in this disease rapidly became widespread. It was soon noted by various observers, beginning with Starr, Segall and Means,[2] that in cases in which this medication was prolonged, its effect, though striking, was usually only temporary; and that after a few weeks the patient might be as ill as before it was started, if not worse. Thus, in general, the prolonged treatment for exophthalmic goiter with iodine alone has come to be regarded as a futile, if not a dangerous, procedure.

There are, however, some observations in the literature concerning favorable results in exophthalmic goiter with this method of treatment. Trousseau,[3] in 1863, mentioned a patient in whom the disease was "singularly improved by the prolonged administration of iodide of potassium." Cheadle,[4] in 1869, reported satisfactory improvement maintained for periods of nine and three months, respectively, in two of seven well marked cases; in none of the other five cases was the disease aggravated. Ohlemann,[5] in 1911, claimed that he was cured

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1. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, J. A. M. A. **80**:1955 (June 30) 1923.

2. Starr, P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.

3. Trousseau, A.: Lectures on Clinical Medicine, translated by P. V. Bazire, London, The New Sydenham Society, 1868, vol. 1, p. 586.

4. Cheadle, W. B.: Exophthalmic Goitre, St. George Hosp. Rep. **4**:175, 1869.

5. Ohlemann: Zur Iodbehandlung bei der Basedow'schen Krankheit, Berl. klin. Wchnschr. **48**:385, 1911.

of exophthalmic goiter after three years' treatment with iodine. Marine and Lenhart,[6] in 1911, observed that complete involution of the thyroid to the colloid state occurred in four patients with exophthalmic goiter who were treated with iodine for periods of from two to eighteen months, and that there were no injurious effects. Neisser,[7] in 1920, reported control of the disease for periods of from one and one-half to two years in three patients. Beebe,[8] in 1921, referring to patients with typical exophthalmic goiter, said that "small doses . . . rarely cause any disturbing reaction and if continued with occasional interruptions over some weeks or months it appears to the writer to be of benefit for the majority." Jagić and Spengler[9] and Mason,[10] in 1924, each noted a similar effect for seven months in one patient; and Cowell and Mellanby,[11] for five months in one of a series of eight patients. Plummer,[12] in 1925, said that some of his patients had been "controlled continuously for more than two years except for short periods during which the administration of iodin was stopped to determine the necessity of continuing it." Mellanby,[13] in 1925, observed that after two years or more of treatment with iodine many patients could lead normal lives and be regarded as cured. He thought that the chief dangers of prolonged iodine medication were in administering it to patients with large hard thyroids. Fraser,[14] in 1925, said that "some patients" would respond satisfactorily to small doses of iodine almost indefinitely, particularly if they could lead sheltered lives; but he found that in most cases the improvement did not persist. Kohlmann,[15] in 1925, noted improvement lasting at least one year in one

6. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment, Arch. Int. Med. **8**:265 (Sept.) 1911.

7. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, Berl. klin. Wchnschr. **57**:461, 1920.

8. Beebe, S. P.: Iodine in the Treatment of Goiter, M. Rec. **99**:996, 1921.

9. Jagić, N., and Spengler, G.: Weitere Beobachtungen über Jodwirkung bei Strumen, Wien. klin. Wchnschr. **37**:116, 1924.

10. Mason, E. H.: Iodine Therapy in Toxic Goitre, Tr. Assoc. Am. Phys. **39**: 167, 1924.

11. Cowell, S. J., and Mellanby, E.: The Effect of Iodine on Hyperthyroidism in Man, Quart. J. Med. **18**:1, 1924-1925.

12. Mayo, C. H., and Plummer, H. S.: The Thyroid Gland, part 2, St. Louis, C. V. Mosby Company, 1926, p. 76.

13. Mellanby, E.: Discussion on the Treatment of Exophthalmic Goitre: Iodine Therapy of Exophthalmic Goitre, Proc. Roy. Soc. Med., Sects. Surg. Med. Electro-Therap. & Therap. **19**:101 (June) 1926.

14. Fraser, F. R.: Iodine in Exophthalmic Goitre, Brit. M. J. **1**:1, 1925.

15. Kohlmann, M.: Kasuistischer Beitrag zur Behandlung des Morbus Basedowii mit kleinen Joddosen, München. med. Wchnschr. **72**:226, 1925.

patient on iodine. Foster,[16] in 1925, remarked that "while some patients continue to take iodine the symptoms and signs of the disease are definitely ameliorated for as long as three years." He regarded the use of iodine as an experiment in each case and said that a systematic study of the question was much to be desired. Labbé,[17] in the same year, in a series of ten cases observed three apparent "cures" during the administration of iodine for a maximum of six months. Cole,[18] in 1927, reported a series of nineteen cases of hyperthyroidism in which iodine was given. Three cases showed no tendency to relapse after continuous treatment for five months. Goetsch,[19] in 1927, said that he had seen a few satisfactory results in very early cases, but that he had abandoned the use of iodine except as a preoperative measure in advanced cases, on account of uniformly bad results.

During the past three years at the Massachusetts General Hospital, we have collected data on a series of twenty-four patients with exophthalmic goiter, most of whom were followed closely with basal metabolism determinations while undergoing prolonged treatment with iodine alone in the outpatient department. These observations seem worth reporting, in view of the present scarcity of such studies.

DATA

The results are summarized in the accompanying table.

Detailed data showing the different types of response are recorded in charts 1 to 10.

In fourteen instances this type of treatment was used because the disease was mild; this group is therefore selected. In the ten others, it was used because, although the disease was moderately severe or severe, operation was at first refused in most instances; this group is, in a sense, unselected.

The Benedict-Roth apparatus and Aub-DuBois standards were used in the determination of the basal metabolic rates. Administration of iodine was not started until two or more determinations which checked satisfactorily were made.

Iodine was used in the form of the compound solution.

16. Foster, N. B.: The Medical Treatment of Hyperthyroidism, Am. J. Surg. **39**:293, 1925.

17. Labbé, M.: Le traitement de la maladie de Basedow par l'iode, J. de méd. de Paris **46**:931, 1926.

18. Cole, L. B.: The Use of Lugol's Iodine in Exophthalmic Goitre, Lancet **1**: 812, 1927.

19. Goetsch, E.: The Use and Misuse of Iodine in the Treatment of Toxic Goiter, New York State J. Med. **27**:1075, 1927.

Response to Prolonged Treatment with Iodine Alone in Twenty-Four Patients with Exophthalmic Goiter

Case	Description	Before Iodine Was Started: Clinical Condition	Before Iodine Was Started: Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Last Observation on Iodine: Clinical Condition	Last Observation on Iodine: Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Duration of Iodine Medication	Comment
1	See chart 1 Lab. No. 3513	Mild exophthalmic goiter	.....	No thyrotoxicosis			
2	See chart 2 Lab. No. 4906	Mild exophthalmic goiter	.....	No thyrotoxicosis			
3	See chart 3 Lab. No. 4034	Mild exophthalmic goiter	.....	No thyrotoxicosis			
4	Miss H. J., a housemaid, aged 19 Lab. No. 5188	Mild exophthalmic goiter; goiter + bruit ++ exophthalmos 0 tremor ++ sweating ++ nervousness +++ weight loss 0	+33, 7 tests Pulse 96 Wt. 56.3 Kg.	No thyrotoxicosis; goiter 0 bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	+16 Pulse 66 Wt. 54.9 Kg.	On compound solution of iodine, from ⅛ to 1 drop daily, continuously, for 5½ months; 9 tests	The basal metabolic rate dropped to +14 per cent within 3 weeks after starting iodine medication; there was marked clinical improvement and gradual disappearance of thyrotoxicosis; when last seen, the patient had been without iodine for 10 months; the basal metabolic rate was +4 per cent and there was no evidence of recurrence of thyrotoxicosis (5 tests)
5	See chart 4 Lab. No. 5663	Mild exophthalmic goiter	.....	No thyrotoxicosis			
6	Mrs. M. H., a housewife, aged 65 Lab. No. 5470	Mild exophthalmic goiter and auricular fibrillation; goiter + bruit 0 exophthalmos +++ tremor + sweating + nervousness ++ weight loss ++	Pulse 106, fibrillating Wt. 40.1 Kg.	No thyrotoxicosis or auricular fibrillation; goiter + bruit 0 exophthalmos + tremor 0 sweating normal nervousness +	Pulse 70, regular Wt. 48.6 Kg.	On compound solution of iodine, 1 drop daily, continuously, for 14 months	Marked improvement in symptoms occurred within 2 weeks after starting iodine; this was sustained throughout the period of iodine medication, in spite of a major pelvic operation. When last seen, the patient had been without iodine for 5½ weeks; there was no evidence of recurrence of thyrotoxicosis; the determinations of basal metabolism (47 tests) were worthless, owing to irregular breathing
7	Miss F. W., a school girl, aged 15 Lab. No. 5530	Mild exophthalmic goiter; goiter + bruit ++ exophthalmos + tremor + sweating ++ nervousness ++ weight loss 0	Dropped from +42 to +14 in 5 weeks (5 tests); +26 later, without iodine Pulse 116 Wt. 44.8 Kg.	No thyrotoxicosis; goiter + smaller bruit 0 exophthalmos + less tremor 0 sweating + nervousness +	+10 Pulse 84 Wt. 48.5 Kg.	On compound solution of iodine, 1 drop daily, for 1 year, with two intervening omissions of 1 month each; 11 tests	On the first two omissions of iodine, the basal metabolic rate rose from normal (−1 and +7 per cent) to +17 and +26 per cent respectively, and there was a recurrence of thyrotoxicosis; during the last course of iodine, of 4 months' duration, the basal metabolic rate again dropped to normal and thyrotoxicosis disappeared; when last seen, the patient had been without iodine for 4 months; the basal metabolic rate was +8 per cent and there was no evidence of thyrotoxicosis (3 tests)

8	See chart 5 Lab. No. 5507	Mild exophthalmic goiter	.....	No thyrotoxicosis			
9	Mrs. V. J., a housewife, aged 41 Lab. No. 5306	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor ? sweating 0 nervousness + + weight loss + +	+23, 3 tests Pulse 106 Wt. 40.5 Kg.	No thyrotoxicosis; goiter 0 bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	—1 Pulse 73 Wt. 40.3 Kg.	Eleven months' continuous administration of compound solution of iodine, ⅛, 1, 5, 1, ⅛ and 1/10 drop daily, respectively (20 tests)	The basal metabolic rate dropped to normal, coincident with the disappearance of thyrotoxicosis, 1 month after iodine was started, and remained there throughout the period of observation
10	See chart 6 Lab. No. 5004	Mild exophthalmic goiter	.....	No thyrotoxicosis			
11	Miss J. O'B., a stenographer, aged 31 Lab. No. 2332	Mild exophthalmic goiter; goiter + + bruit 0 exophthalmos + tremor + sweating + nervousness + + weight loss +	+36 Pulse 104 Wt. 47.8 Kg.	No thyrotoxicosis; goiter + bruit 0 exophthalmos + tremor 0 sweating normal nervousness +	+6 Pulse 89 Wt. 46.7 Kg.	Eleven months' continuous administration of iodine, either 1 drop of compound solution or 0.75 Gm. of potassium iodide daily in asthma medicine; sometimes both (4 tests)	Up to 9 months after starting iodine the basal metabolic rate had dropped to only + 21 per cent (3 tests); about 3½ years before this period of observation, the patient had questionable exophthalmic goiter, with a basal metabolic rate of + 24 per cent; during 1 month of iodine medication there was no improvement; on omission of iodine, the basal metabolic rate rose to + 43 per cent and there was definite thyrotoxicosis; about 3 months later the basal metabolic rate was — 16 per cent and there was no evidence of thyrotoxicosis; she was not seen again for 3 years
12	Miss S. G., a school girl, aged 18 Lab. No. 5092	Mild exophthalmic goiter; goiter + + bruit + + exophthalmos + tremor + sweating + + nervousness + + weight loss 0	+22, 3 tests Pulse 98 Wt. 41.9 Kg.	No thyrotoxicosis; goiter slightly + bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	+4 Pulse 93 Wt. 42.1 Kg.	On compound solution of iodine, usually 1 drop daily, for 1⅔ years, with 2 omissions of 2 months each (21 tests)	During the first 3 months on iodine the basal metabolic rate did not drop, but the patient gained 3 Kg. and was slightly improved; on omission of iodine for 2 months, the basal metabolic rate rose to + 40 per cent, the pulse to 124, and her weight dropped 2 Kg.; on resuming iodine medication, the basal metabolic rate promptly dropped to + 15 per cent, with definite clinical improvement, remaining thus for about 10 months until iodine was omitted; then the basal metabolic rate rose to + 26 per cent and she became more nervous; on resuming iodine, the rate dropped to + 4 per cent; there was no evidence of thyrotoxicosis
13	Mr. R. S., a gardener, aged 46 Lab. No. 5398	Moderately severe exophthalmic goiter; goiter * sweating + + + nervousness + + weight loss + + + appetite + + Palpitation and dyspnea +	+40, 2 tests Wt. about 70 Kg.	Very mild exophthalmic goiter; goiter + bruit 0 exophthalmos 0 tremor 0 sweating + nervousness +	+21 Pulse 70 Wt. 78.6 Kg.	One year continuously on compound solution of iodine, 30 drops daily, and then 30 drops daily twice a week (2 tests)	Marked improvement in symptoms and a gain of 20 pounds in weight occurred within 3 months after starting iodine; the patient was first seen in this clinic about 10 months after starting iodine; the basal metabolic rate was + 25 per cent, but the patient showed little evidence of thyrotoxicosis

* Size unknown.

Response to Prolonged Treatment with Iodine Alone in Twenty-Four Patients with Exophthalmic Goiter—(Continued)

Case	Description	Before Iodine Was Started: Clinical Condition	Before Iodine Was Started: Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Last Observation on Iodine: Clinical Condition	Last Observation on Iodine: Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Duration of Iodine Medication	Comment
14	Mrs. E. C., a housewife, aged 35 Lab. No. 4675	Mild exophthalmic goiter; goiter + bruit + exophthalmos + tremor + sweating + nervousness ++ weight loss ++	+24, 2 tests Pulse 104 Wt. 47.9 Kg.	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor + sweating + nervousness ++	+19 Pulse 87 Wt. 49.0 Kg.	There were 3 courses of compound solution of iodine, of 1, 4 and 9 months' duration respectively, with 2 intervening omissions of 2 months each; the dose varied from ½ to 30 drops daily (36 tests)	The first course of compound solution of iodine had little clinical effect; the basal metabolic rate dropped to + 15 per cent and rose, on omission of iodine, to + 26 per cent; the second course of iodine had a prompt and striking effect, finally producing a clinical condition suggesting mild myxedema, with a basal metabolic rate of — 15 per cent; on omission of iodine, the basal metabolic rate rose to + 21 per cent and thyrotoxicosis recurred; during the third course of iodine the basal metabolic rate promptly fell to normal, with some clinical improvement; the patient remained thus for about 7 months; during the next 2 months on iodine the basal metabolic rate rose to + 19 per cent and the patient felt as ill, but no worse, than before iodine medication was started
15	Mrs. A. H., a housewife, aged 37 Lab. No. 5917	Mild exophthalmic goiter; goiter ++ bruit + exophthalmos + tremor + sweating ++ nervousness ++ weight loss +	Dropped from +26 to +12 on rest in bed; 4 tests Pulse 72 Wt. 45.8 Kg.	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor 0 sweating + nervousness +	+17 Pulse 75 Wt. 47.1 Kg.	On compound solution of iodine, from 30 to 5 drops daily, for 1½ months continuously (4 tests)	The basal metabolic rate fell to — 7 per cent, with corresponding clinical improvement, while the patient was in the hospital, within 1 week after starting iodine; the patient was then discharged; about 5 weeks later her basal metabolic rate was + 17 per cent and thyrotoxicosis was recurring (only on omission of iodine did the basal metabolic rate rise to 46 per cent and the patient become worse than initially)
16	Mr. E. S., a factory worker, aged 35 Lab. No. 6251	Moderately severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor + sweating ++ nervousness +++ weight loss ++	+50, 3 tests Pulse 98 Wt. 55.5 Kg.	Moderately severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor + sweating + nervousness +++	+44 Pulse 96 Wt. 55.7 Kg.	About 3 months continuously on compound solution of iodine, 1 drop daily (6 tests)	The basal metabolic rate fell to +13 per cent with definite clinical improvement within 2 weeks after starting iodine; it then rose gradually to +57 per cent within another 5 weeks, before dropping to the final +44 per cent; thyrotoxicosis recurred, but the patient was no worse at any time than before iodine was started
17	Miss A. P. Y., a factory worker, aged 21 Lab. No. 4822	Severe exophthalmic goiter; goiter ++ bruit ++ exophthalmos 0 tremor + +	+72, 2 tests Pulse 131 Wt. 51.7 Kg.	More severe exophthalmic goiter; goiter ++ bruit +++ exophthalmos 0 tremor + + +	+80 Pulse 122 Wt. 56.1 Kg.	4½ months continuously on compound solution of iodine, 1, 15, 30, 1, 30, 90 and 1 drop daily, respectively (33 tests)	The basal metabolic rate fell to +27 per cent within 10 days after starting 1 drop of compound solution of iodine; about 3 weeks later, on 30 drops, it fell to +16 per cent; there was marked clinical improvement; after this the basal metabolic rate gradually rose on 30 drops and continued to rise

		sweating ++ nervousness ++ weight loss ++		sweating +++ nervousness +++			on 1 drop of compound solution of iodine until, 3 months after starting iodine medication, it was +58 per cent; on 30 and 90 drops, it fell to +33 per cent, but on reducing the dose 3 weeks later to 1 drop, it gradually rose to +80 per cent; at this point the thyrotoxicosis was more marked than before iodine was started; the patient was completely refractive to 1 drop of compound solution of iodine daily, because when this was omitted, the basal metabolic rate did not rise significantly, but within 2 months decreased spontaneously to +65 per cent; at this time 1 drop of compound solution of iodine daily produced a typical remission
18	See chart 7 Lab. No. 5168	Moderately severe exophthalmic goiter	.....	Severe exophthalmic goiter			
19	See chart 8 Lab. No. 6414	Moderately severe exophthalmic goiter	.....	Severe exophthalmic goiter			
20	Mrs. E. O., a housewife, aged 52 Lab. No. 5668	Moderately severe exophthalmic goiter; goiter + very firm bruit 0 exophthalmos 0 tremor ++ sweating +++ nervousness +++ weight loss ++	+38, 6 tests Pulse 100 Wt. 57.0 Kg.	Moderate but less severe exophthalmic goiter; goiter + very firm bruit 0 exophthalmos 0 tremor 0 sweating ++ nervousness ++	+29 Pulse 91 Wt. 61.6 Kg.	7½ months on compound solution of iodine, from ½ to 1 drop daily, with one omission of 1½ months (8 tests)	The symptomatic improvement on compound solution of iodine was gradual and sustained, in spite of an intercurrent illness, but was not sufficient to be satisfactory; all basal metabolic rate determinations but one (+23 per cent), during iodine medication, were +29 per cent and above
21	Mr. A. B., a telegrapher, aged 35 Lab. No. 6312	Moderately severe exophthalmic goiter; goiter + bruit ? exophthalmos 0 tremor + sweating ++ nervousness ++ weight loss ++	Dropped from +45 to +29 on rest in bed; 6 tests Pulse 102 Wt. 51.9 Kg.	Moderate but less severe exophthalmic goiter; goiter + bruit 0 exophthalmos 0 tremor + sweating + nervousness +	+37 Pulse 101 Wt. 57.9 Kg.	On compound solution of iodine, from 1 to 2 drops daily, for 2 months continuously (4 tests)	Iodine was started on discharge from the hospital; within 2 weeks, although the basal metabolic rate was unchanged (+28 per cent), the patient had gained 5 Kg., was less nervous and slept better; 2 weeks later the basal metabolic rate was +35 per cent, and he had gained an additional 2 Kg.; the basal metabolic rate did not fall below this level subsequently, and he did not gain any more weight
22	See chart 9 Lab. No. 6102	Severe exophthalmic goiter	.....	Less severe exophthalmic goiter			
23	Mr. I. C., a salesman, aged 41 Lab. No. 5967	Severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor + sweating + nervousness ++ weight loss ++	+57, 12 tests Pulse 114 Wt. 70.9 Kg.	More severe exophthalmic goiter; goiter + bruit ++ exophthalmos ++ tremor ++ sweating +++ nervousness +++	+77 Pulse 113 Wt. 68.2 Kg.	On 1 drop of compound solution of iodine daily for 3 months continuously (5 tests)	The basal metabolic rate did not drop significantly on compound solution of iodine, but gradually rose; the thyrotoxicosis became more marked; on omission of iodine for 9 days, the basal metabolic rate remained practically unchanged; compound solution of iodine then reduced it to +42 to +52 per cent and the patient was operated on
24	See chart 10 Lab. No. 5181	Severe exophthalmic goiter	.....	More severe exophthalmic goiter			

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Types of Response.—Satisfactory: Nine cases responded satisfactorily to prolonged iodine medication as follows:

1. In four the disease apparently came to an end during or shortly after the period of treatment with iodine. This is indicated by the fact that for periods of from ten to sixteen months after iodine was omitted, the basal metabolic rate remained at a standard normal level or below and there was no clinical evidence of recurrence of thyrotoxicosis (cases 1, 2, 3 [charts 1, 2 and 3] and 4 [table]).

2. In the five others, during periods of continuous iodine medication ranging from ten to fourteen months in four cases and from one to four months intermittently for one year in one case, the disease

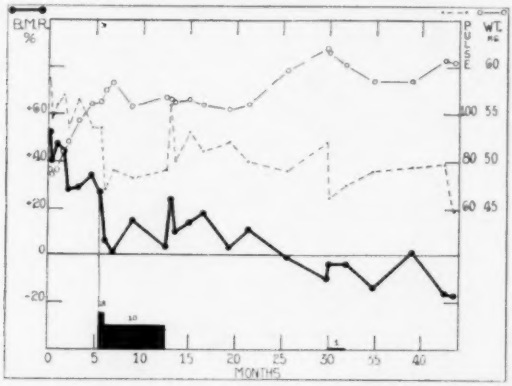

Chart 1 (case 1, lab. no. 3513).—Mrs. A. V. B., a housewife, aged 25, in whom control of signs and symptoms of mild exophthalmic goiter was secured by administration of iodine for seven months during a spontaneous retrogression of the disease (which did not appear to be hastened by the medication). At the time treatment with iodine was started: goiter +, bruit 0, exophthalmos +, tremor +, sweating +, nervousness ++. At the time of the last observation on iodine: thyroid just palpable, bruit 0, exophthalmos 0, tremor very slight, sweating normal, nervousness +. From five to seven months after omitting the first course of iodine there was no tremor and the patient was not nervous. She remained normal during the rest of the period of observation. In this and the accompanying charts, the black areas along the bottom indicate periods of treatment with compound solution of iodine and the figures above them the dosage in drops.

was at least kept satisfactorily under control with a normal basal metabolism (cases 5 [chart 4], 6, 7 [table], 8 [chart 5] and 9 [table]). In the first three cases iodine was omitted for four, five and seventeen weeks respectively, with no recurrence of symptoms; in the last two cases it was not omitted.

Fairly satisfactory: In four cases the response to prolonged iodine medication was fairly satisfactory. The results may be summarized as follows:

1. During continuous iodine medication for one and two-thirds years, the disease was again under control with a normal basal metabolism, after two prolonged complete remissions and two mild relapses (case 10 [chart 6]).

2. The disease was satisfactorily controlled, with a normal basal metabolism, only after nine months of continuous iodine medication in one case, and after eighteen months of intermittent iodine medication in another. However, during most of the periods of incomplete control, the patients were markedly improved and at no time did they become worse on iodine (cases 11 and 12 in table).

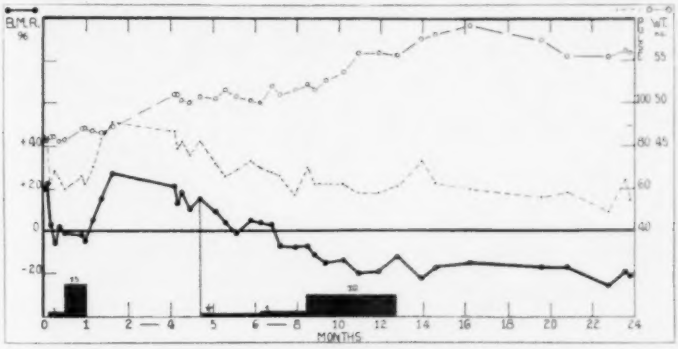

Chart 2 (case 2, lab. no. 4906).—In Mrs. E. F., a housewife, aged 28, there was control of signs and symptoms of mild exophthalmic goiter during the first course of iodine medication, and disappearance of the disease during the second course of iodine. At the time the first course of iodine was started: goiter +, bruit +, exophthalmos ++, tremor +, sweating +, nervousness ++, weight loss ++. At the time of the last observation on the second course of iodine: thyroid just palpable, bruit 0, exophthalmos 0, tremor 0, sweating normal, nervousness +. She was apparently normal during the rest of the period of observation.

3. During one year of continuous iodine medication, there was an initial prompt and striking remission which was sustained but not quite complete. The basal metabolism did not drop below plus 21 per cent (case 13 in table).

Unsatisfactory: In eleven cases the response to prolonged iodine medication was unsatisfactory. These cases can be grouped as follows:

1. In six there was a temporary improvement, accompanied by a lowering of the basal metabolism, followed by a relapse (cases 14, 15,

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16, 17 [table], 18 [chart 7] and 19 [chart 8]). In all but case 14 the improvement was of short duration. Patients 17, 18 and 19 were worse symptomatically and had a higher metabolism during the relapse than before iodine was started.

2. In three there was a gain in weight and some symptomatic improvement, but no significant change in the basal metabolic rate (cases 20, 21 [table] and 22 [chart 9]).

3. In two there was no clinical improvement and no significant decrease, but a gradual increase in the basal metabolic rate, with coincident increase in the severity of symptoms (cases 23 [table] and 24 [chart 10]).

Thus, in our series of twenty-four cases, over half of which were selected because they were mild, the results obtained during prolonged

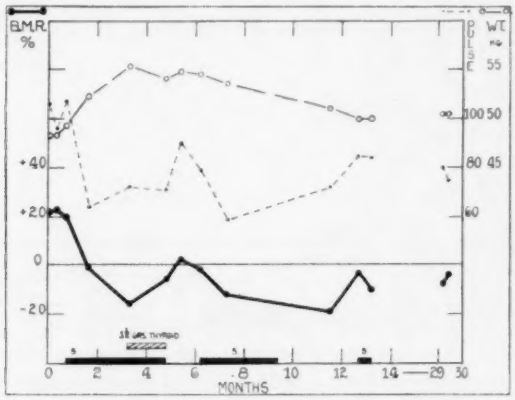

Chart 3 (case 3, lab. no. 4034).—In Miss F. K., a dentist's secretary, aged 17, mild exophthalmic goiter disappeared during prolonged iodine medication. At the time the first course of iodine was started: goiter ++, bruit ++, eyes staring, tremor 0, sweating +, nervousness ++, weight loss +. At the time of the last observation on the second course of iodine: goiter +, bruit 0, eyes slightly staring, tremor 0, sweating normal, nervousness +. The patient remained thus during the rest of the period of observation.

iodine medication were satisfactory in 37 per cent, fairly satisfactory in 17 per cent and unsatisfactory in 46 per cent.

Initial Severity of the Disease.—All nine patients (cases 1 to 9) who responded satisfactorily presented the disease in mild form. In all but one of the four patients (cases 10 to 13) who responded fairly satisfactorily the disease also occurred in a mild form: in case 13 the disease was moderately severe. In the group of eleven patients who did not respond satisfactorily, two had mild cases initially (cases 14

and 15), five moderately severe (cases 16, 18, 19, 20 and 21) and four severe (cases 17, 22, 23 and 24).

Thus in the fourteen mild cases, satisfactory results were obtained in 64 per cent, fairly satisfactory results in 22 per cent and unsatisfactory results in 14 per cent, in contrast to the ten severe and moderately severe cases in which there were no satisfactory results, fairly satisfactory results in only 10 per cent (one case), no permanent satisfactory benefit in 40 per cent and aggravation of symptoms in 50 per cent.

Miscellaneous Factors.—The data on the relation of the age of the patient, the duration of the disease, the consistency and size of the goiter and the presence of a bruit to the type of response to iodine are not extensive enough to warrant definite statements. As far as

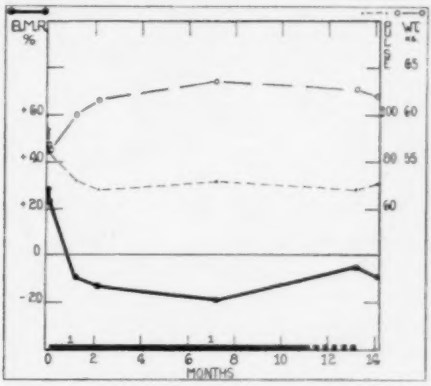

Chart 4 (case 5, lab. no. 5663).—In Mr. E. D., an x-ray technician, aged 49, control of and apparent disappearance of mild exophthalmic goiter were secured during prolonged iodine medication. At the time iodine was started: goiter +, bruit 0, exophthalmos +, tremor ++, sweating +, nervousness ++, weight loss ++. At the time of the last observation on iodine: goiter 0, bruit 0, exophthalmos less, tremor 0, sweating normal, nervousness 0. Following the omission of iodine, symptoms did not recur.

they go, they do not show that any of these factors has an important bearing on the results of prolonged iodine medication. There is a suggestion that the larger and firmer the thyroid gland, the less satisfactory the outcome with such treatment.

COMMENT

It is of interest to compare our results with prolonged iodine treatment in this series with those noted in similarly treating a group of patients who had thyrotoxicosis following a "subtotal" thyroidectomy

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for exophthalmic goiter.[20] In ten of thirty-seven such patients its use was not continued long enough to determine the response. Eleven of the remaining twenty-seven patients, with basal metabolisms ranging from plus 20 to plus 45 per cent after operation, showed a satisfactory response to prolonged iodine medication; eight showed a fair response, and eight a poor response. In six of the eight patients who showed a poor response, a large amount of palpable thyroid tissue was noted and the disease was present in at least a moderately severe form. The group of eleven who responded well included ten with mild cases and one with a moderately severe case.

Thus our experiences with the postoperative group and with the group concerned in this paper have led us to believe that a certain number of patients with exophthalmic goiter can be satisfactorily

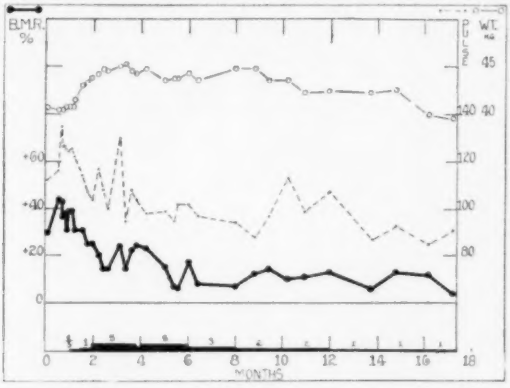

Chart 5 (case 8, lab. no. 5507).—In Miss M. C., a high school girl, aged 19, control of mild exophthalmic goiter was secured during prolonged continuous treatment with iodine alone. At the time iodine was started: goiter +, bruit +, exophthalmos 0, tremor 0, sweating+, nervousness +++, weight loss +. At the time of the last observation on iodine: goiter +, bruit 0, exophthalmos 0, tremor 0, sweating normal, nervousness +.

treated with iodine alone. At present there is no way of predicting definitely in any given case what the response to such treatment will be. Our data indicate that the single most important criterion may be the severity of the disease, mild cases usually doing well and severe or moderately severe cases usually showing no more than temporary improvement. The marked reduction in the intensity of the disease as a result of operation would appear to explain the large number of

20. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, to be published.

satisfactory results from this treatment in patients who have thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter.

Nevertheless, the severity of the disease at any given time is not the only consideration, as shown by the fact that even mild cases may occasionally become worse, and in a few instances a moderately severe case may do well during prolonged iodine administration. Inasmuch as the severity of the disease may vary markedly in the same patient from time to time, it is reasonable to suppose that the manner in which the disease is progressing spontaneously is important in determining the response. For example, it may be: (1) decreasing in severity and in a mild state when iodine medication is started; (2) increasing in severity from a mild to a more severe state before treatment with iodine is started, or (3) mild throughout its course, whether stationary or fluctuating in severity from time to time. Unfortunately,

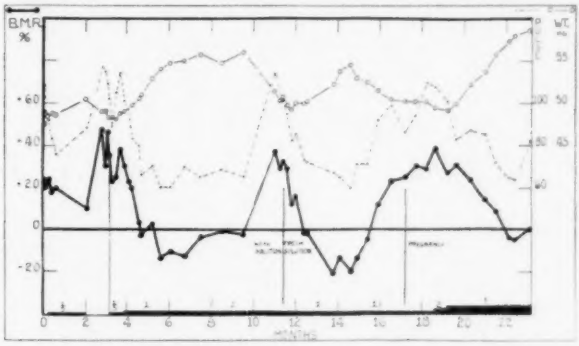

Chart 6 (case 10, lab. no. 5004).—In Mrs. M. P. W., a housewife, aged 20, there were three remissions and two mild relapses of mild exophthalmic goiter during continuous prolonged administration of iodine (preceded by a mild relapse on omission of the first course of iodine). The first relapse during the administration of iodine was possibly caused by weakening of the medicine. The second relapse on iodine was of unknown origin, but the disease may have been aggravated by the general malaise of the first few months of pregnancy. Improvement was coincident with the disappearance of nausea and vomiting. At the time the first course of iodine was started: goiter ++, bruit ++, exophthalmos +, (?) slight tremor, sweating +, nervousness ++, weight loss +. At the time of the last observation on iodine: goiter +, bruit 0, exophthalmos +, tremor 0, sweating normal, nervousness 0.

information of this type is rarely available, owing to the usual lack of time necessary for such observation before iodine medication is started. It is our impression that most of the patients in whom satisfactory or fairly satisfactory results were noted belong in groups 1 and 3.

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The hypothesis that the natural course of the disease, i. e., whether fluctuating or stationary, and the intensity with which it is acting are important factors in determining the nature of the response to prolonged iodine medication is upheld by the observations on the following three cases:

Case 1 (chart 1) illustrates clearly an instance in which the natural course of the disease was the important factor in recovery. There had been a gradual spontaneous clinical improvement, accompanied by a drop in basal metabolism from plus 53 per cent to plus 27 per cent and a gain in weight from 49 to 56 Kg. for about six months before the seven months' course of iodine was started; but the disease apparently did not disappear completely until about five months after iodine was omitted. During the subsequent two years the patient presented no evidence of recurrence of thyrotoxicosis. Thus, in this case, iodine

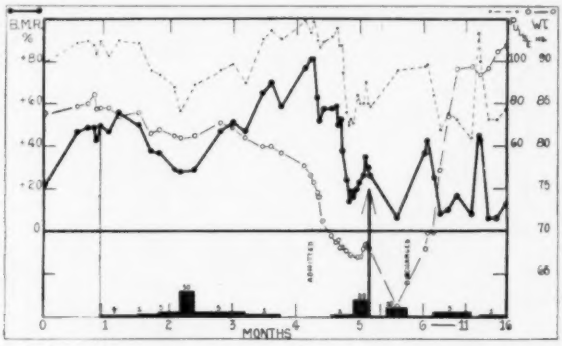

Chart 7 (case 18, lab. no. 5168).—In Mrs. E. H., a housewife, aged 26 years, slight improvement followed by an increase in severity of moderately severe exophthalmic goiter was noted during the continuous administration of iodine (first course). A further increase in severity occurred on omission of iodine with subsequent typical remission during administration of 1 drop of compound solution of iodine daily, just preceding subtotal thyroidectomy (arrow). Note that the disease was increasing in severity before treatment with iodine was started. At the time the first course of iodine was started: goiter ++, bruit ++, exophthalmos 0, tremor 0, sweating +, nervousness +, weight loss +++. At the time of the last observation on the first course of iodine: goiter ++, bruit +, exophthalmos +, tremor +, sweating +, nervousness ++.

can be credited only with holding the disease in check during the course of natural recovery. Complete recovery took place within three years after the onset of the disease (which was from one to two years before the patient was first seen in this clinic). Whether this was hastened or delayed by iodine is unknown.

In striking contrast to case 1 is case 18 (chart 7). As may be judged from the chart, the disease spontaneously changed from mild

to moderate severity in association with an increase in basal metabolism from about plus 22 per cent to about plus 50 per cent before treatment with iodine was begun. While iodine was still being administered, the patient, after showing an initial improvement, became slightly worse than before it was started, and when it was omitted, a little worse still. Thus, when the disease appeared to be getting worse spontaneously, iodine checked the increase in severity only temporarily.

In case 10 (chart 6) there were two relapses followed by remissions during the continuous administration of small doses of compound solution of iodine. At the time of the first relapse it was noted that the compound solution of iodine had become weaker.[21] The patient was taking only one drop daily (about 6 mg. of iodine); we have observed that this is about the minimum dose that will produce a maximum

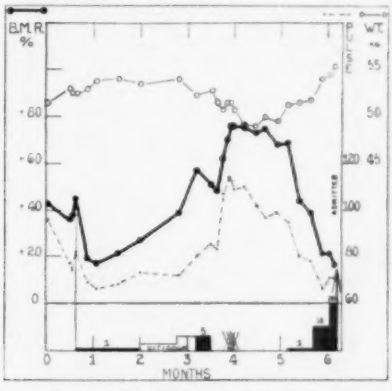

Chart 8 (case 19, lab. no. 6414).—In Mrs. E. R., a housewife, aged 34, during the continuous administration of iodine (first course) a remission was followed by an increase in the severity of exophthalmic goiter which was initially moderately severe. A further increase in severity occurred on omission of iodine. There was very slight clinical improvement from roentgen treatment (×) within one month. Iodine then produced a typical remission just preceding subtotal thyroidectomy (arrow). At the time that the first course of iodine was started: goiter +, bruit +, exophthalmos ++, tremor +, sweating +, nervousness ++, weight loss ++. At the time of the last observation on the first course of iodine: goiter ++, bruit ++, exophthalmos ++, tremor +, sweating ++, nervousness +++.

21. At the time the compound solution of iodine was noted to be weak, it was being kept in a cork-stoppered bottle. Under these circumstances a reaction takes place between the cork and the solution, as a result of which the cork is slowly destroyed and the solution becomes much paler. This does not occur if the solution is kept in a glass-stoppered bottle. This case has been reported in detail from the standpoint of the low metabolism in a paper by Thompson, Thompson, Brailey and Cohen, see footnote 22.

22. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Myxedema During the Administration of Iodine in Exophthalmic Goiter, Am. J. M. Sc., to be published.

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reduction in basal metabolism in most cases of exophthalmic goiter in Boston.[23] Shortly after the same dose of fresh solution was substituted, the basal metabolism began to drop. An inadequate intake of iodine may therefore well account for the first relapse during this medication. The second relapse, however, would appear to have a different explanation. Thyrotoxicosis had gradually recurred about one month before the patient became pregnant. This time the solution of iodine had lost only slightly in strength and the substitution of fresh solution was without effect. Similarly, tripling the dose of the fresh solution (three drops daily) did no good. Some degree of general malaise may have been the cause of the aggravation of symptoms observed

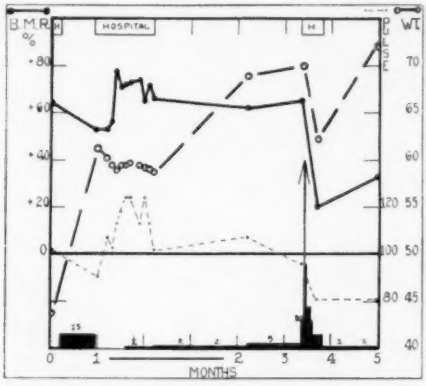

Chart 9 (case 22, lab. no. 6102).—Mr. J. C., a gardener-caretaker, aged 40, showed no significant drop in basal metabolic rate, yet a marked gain in weight and some clinical improvement in severe exophthalmic goiter during prolonged administration of iodine. At the time that the first course of iodine was started: goiter +, bruit ++, exophthalmos +, tremor ++, sweating ++, nervousness +++, weight loss +++. At the time of the last observation on the second course of iodine, that is, shortly before subtotal thyroidectomy (arrow): goiter ++, bruit 0, exophthalmos ++, tremor 0, sweating +, nervousness ++.

23. Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exopthalmic Goiter, J. A. M. A. **91**:1719 (Dec. 1) 1928. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, Arch. Int. Med., in press. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, Arch. Int. Med., in press. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, Arch. Int. Med., in press.

for the first three months of pregnancy, during which time she had morning nausea and vomiting. As her general condition improved, her metabolism fell to normal and her thyroid gland became a little smaller and softer. The first relapse on iodine lasted from one to two months, and the second one, five months. It is of interest that at no time during either relapse did the basal metabolism go quite as high as it previously had when iodine was omitted. Presumably, a portion of the thyrotoxicosis was being held in check in spite of the relapse. During all three relapses (one without and two with iodine medication) the thyrotoxicosis was only mild, and it seems probable that in this

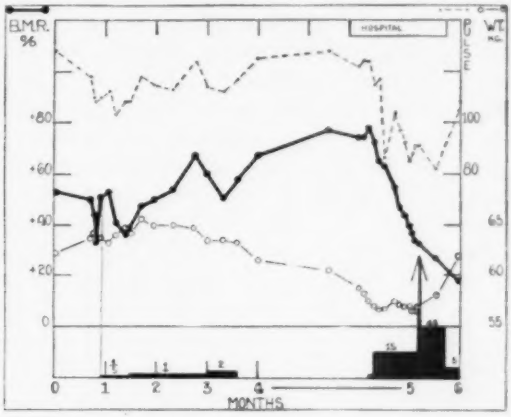

Chart 10 (case 24, lab. no. 5181).—Miss M. K., an office worker, aged 23, showed an increase in the severity of severe exophthalmic goiter, without any initial improvement, during the prolonged administration of iodine, and further increase in severity on omission of iodine. A subsequent typical remission occurred during the administration of iodine just before subtotal thyroidectomy (arrow). At the time that iodine medication was started: goiter ++, bruit ++, exophthalmos +, tremor ++, sweating +++, nervousness ++, weight loss ++. At the time of the last observation on the first course of iodine: goiter ++, bruit +, exophthalmos +, tremor +++, sweating +++, nervousness +++.

patient the disease may be held satisfactorily in check by iodine until it terminates.

Thus there are cases in which iodine does not appear to interfere with either the disappearance of the disease or an increase in its severity, and cases which show a spontaneous relapse followed by a remission during the continuous administration of iodine. In short, the response of patients with exophthalmic goiter to iodine appears to be determined not by the iodine, but by what is happening to the disease itself. The theory that iodine acts more as a check on the effects of the disease rather than as the remover of its cause has been

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advanced in previous communications from this clinic.[24] While the bulk of the present data is consistent with such a view, the possibility remains that in cases in which the disease is acting with great intensity, iodine may sometimes aid the aggravation of symptoms by furnishing in excess one of the raw materials out of which a still greater amount of thyroxin may be made. This may be the explanation of the fact that five of our patients became worse during the administration of iodine although in them, as well as in the patients with mild cases who did well during this treatment, the natural course of the disease must be considered. In two patients (case 23 in table; case 24, chart 10) there was no improvement at any time, but a gradual increase in the severity of the signs and symptoms. This could be attributed to a natural increase in the severity of the thyrotoxicosis, over which iodine did not have even its usual temporary control. In three cases (case 17, table; case 18, chart 7; case 19, table) there was temporary improvement, but as the effect of iodine wore off, the patients were worse than before it was started. This, too, could be attributed to a natural increase in the severity of the disease, which iodine was finally unable to control. The increases in intensity were so marked and abrupt, however, that it seems possible that iodine may at least have been a factor in their production. There is much in the literature to the effect that prolonged iodine medication may aggravate the disease. If one may judge by the quantity of the reports and the acknowledged acumen of many of the authors, there must be some truth in the statement. However, the lack of a good control series of untreated cases is a serious obstacle to accepting this impression for fact.

It is hard to understand why in mild cases improvement will often continue as long as iodine is administered, whereas in severe cases it is usually only temporary and a stage is reached in which the disease may be worse than before iodine was started and the portion of the thyrotoxicosis still controlled by iodine smaller than initially. Indeed one of the patients in this series (case 17 in table) became completely refractory to one drop of compound solution of iodine daily during the continuous administration of iodine, and after a short period of freedom from iodine, showed a marked reduction in basal metabolism on this dose. It would seem that if the disease is acting with great intensity it can at least partially overcome the beneficial effect of iodine, whereas if it is acting only with mild intensity it cannot.

24. Means, J. H.; Thompson, W. O., and Thompson, P. K.: On the Nature of the Iodine Reaction in Exophthalmic Goiter: With Particular Reference to the Effect of Iodine Late in the Course of the Disease, Tr. A. Am. Phys. **43**:146, 1928. Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 151.

The percentage of unselected cases of exophthalmic goiter that will show a satisfactory response to prolonged iodine medication is unknown, but is probably small. We wish to emphasize that the results in our series do not represent the results to be expected in an unselected group, inasmuch as the majority were selected because they had the disease in mild form. There would appear to be little virtue in trying to treat patients with moderately severe or severe forms of the disease in this manner. If the effect of this treatment were to be judged by the response in an unselected group of cases, without reference to the severity of the disease, the results usually would be so poor that prolonged iodine medication would be regarded as too dangerous a method of treatment to employ in any type of case. By limiting this treatment to mild cases, however, a high percentage of satisfactory results probably would be secured and little damage done. It is perhaps needless to add that patients should be examined and have their basal metabolisms determined about once a month throughout the period of observation. Moreover, before treatment is begun, patients should be told that its results are uncertain and that an operation eventually may be necessary.

What effect iodine has on the duration of the disease in the cases responding satisfactorily is unknown. To determine this, it is necessary to have accurate statistics regarding the course of the disease in untreated patients. Unfortunately, none are available. Hyman and Kessel's [25] series of patients, while purporting to show the "spontaneous course," was treated mainly by rest and also by iodine. Hale-White's [26] and Campbell's [27] patients were treated by rest and also in some instances by "galvanism" or by roentgen rays. From isolated observations, however, it is known that in a certain number of cases of exophthalmic goiter the disease will disappear without treatment in the course of a few years.

In the four cases in which the disease came to an end (cases 1, 2 and 3, charts 1, 2 and 3; case 4 in table), iodine may have acted in any of three ways:

1. It may have merely held the disease in check until a spontaneous recovery took place, which was not hastened by this treatment.

2. While holding the disease in check, it may have hastened spontaneous recovery.

25. Hyman, H. T., and Kessel, L.: Studies of Exophthalmic Goiter and the Involuntary Nervous System: X. The Course of the Subjective and Objective Manifestations in Fifty Unselected Patients Observed Over a Period of Two Years, in Whom no Specific Therapeutic Measures Were Instituted ("Spontaneous Course"), Arch. Surg. **8**:149 (Jan.) 1924.

26. Hale-White, W.: The Outlook of Sufferers from Exophthalmic Goitre, Quart. J. Med. **4**:89, 1910.

27. Campbell, J. M. H.: Some Aspects of Exophthalmic Goitre, Quart. J. Med. **15**:55, 1921-1922.

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3. It may have instigated a recovery which otherwise would not have taken place.

In the remaining cases showing a satisfactory response, iodine has not been omitted for a sufficient length of time to draw conclusions as to whether the disease is retrogressing or has disappeared. All that can be said is that iodine held the symptoms efficiently in check for long periods, usually for more than a year (cases 5 and 8, charts 4 and 5; cases 6, 7 and 9 in table). Aside from this, what influence it has had on the course of the disease in the meantime is a matter of conjecture.

While iodine may have more far-reaching effects in mild exophthalmic goiter, even the fact that it usually produces an abrupt remission and at least holds the disease in check while it is pursuing its natural course, makes it a valuable method of treatment in this type of case.

The usual striking effect of rest in bed emphasizes the importance of eliminating this factor when judging the effect of iodine alone in the treatment for exophthalmic goiter. For this reason we wish to stress the fact that ours was essentially an outpatient series. There were three exceptions (cases 15 and 21 in table; case 22, chart 9). Iodine medication was started on discharge of the patient from the hospital. Thus the change from rest to activity may have been a factor in the unsatisfactory response to iodine. Recovery or remission in all the cases showing satisfactory results took place during the stress of the patient's customary routine. For example, patient 8 (chart 5), a naturally high-strung girl, continued her junior and senior high school work during the period of observation. Previous to treatment she had taken part in a play and had broken down completely in the first act. After she had been given iodine continuously for about a year, she took a leading part in another play. She acted her part well and did not suffer from undue nervousness either during rehearsals or in the actual performances. During treatment, patients 5 (chart 4), 11 and 13 (table) continued their occupations of x-ray technician, stenographer and gardener, respectively. In patient 6 (table) the control of signs and symptoms of thyrotoxicosis, including the disappearance of auricular fibrillation, was maintained in spite of the emotional strain resulting from life with a rather worthless husband, and in spite of a major pelvic operation. The other patients had the usual amount of housework to perform.

Some observers are of the opinion that small doses are less liable to do harm during prolonged medication than are large doses.[28] While

28. Beebe (footnote 8). Cowell and Mellanby (footnote 11). Fraser (footnote 14). Cole (footnote 18). Marine, D.: Iodin in the Treatment of Diseases of the Thyroid Gland, Medicine **6**:127, 1927.

in our series the customary dose has been comparatively small, i. e., one drop of compound solution of iodine (about 6 mg. of iodine) daily, in instances in which it was administered for a time in much larger doses, even as much as ninety drops daily (case 17, table), there was no proof that the increase had an aggravating effect. Patient 16 (table), while not receiving any more than one drop daily, after striking temporary improvement had a relapse on this dose. The data suggest that the response to iodine in exophthalmic goiter is determined not by the size of the dose, as long as it is large enough to produce a maximum effect, but by something fundamental about the disease, presumably related to its cause, over which iodine exercises no control. Undoubtedly small doses are more palatable than large doses. For this reason, during prolonged medication, we generally use approximately the smallest dose which will produce a maximum effect on basal metabolism. In Boston, this appears to be about one drop of compound solution of iodine daily.[23]

SUMMARY

Twenty-four patients with exophthalmic goiter (fourteen mild and ten severe or moderately severe cases) have been treated in this clinic with iodine alone, either continuously or intermittently for periods ranging from one and one-half months to three years. The period of treatment was a year or more in thirteen instances.

With three exceptions (all unsatisfactory responses to iodine) the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest.

In nine of the fourteen mild cases (64 per cent) the results were satisfactory; i. e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In four of these nine cases (in which iodine was omitted from ten to sixteen months) the disease has apparently disappeared, and in three others in which it has been omitted from four to seventeen weeks, there has been no recurrence of symptoms. In three of the fourteen mild cases (22 per cent) the results were fairly satisfactory; i. e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory; the disease did not become worse, however, on iodine.

In the ten severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in four (40 per cent), and the disease became worse in five (50 per cent).

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CONCLUSIONS

Patients with moderately severe or severe exophthalmic goiter rarely show more than temporary improvement during the prolonged administration of iodine. Frequently the disease becomes more severe than before iodine was started.

If the disease is mild, however, the patients often respond satisfactorily, and in some patients it terminates. The proportion of unsatisfactory results in Boston appears to be so small that it is not a contraindication to prolonged treatment with iodine if strictly confined to mild cases and if the patients are kept under close observation.

The response of patients with exophthalmic goiter to prolonged iodine medication appears to be determined more by what is happening to the disease spontaneously than by the iodine itself. In the cases showing satisfactory results, iodine may have merely held the disease in check while it was pursuing its natural course. Even this, however, makes it valuable in the treatment for mild exophthalmic goiter.

THE SIZE OF THE HEART IN EXPERIMENTAL HYPERTHYROIDISM *

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AND
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Accurate data concerning the effect of hyperthyroidism on the size of the heart do not appear to be available in the literature. Not only is the heart rate markedly increased in this condition but, according to Samson Wright,[1] the stroke volume in exophthalmic goiter averaged 116 cc., as compared with the normal of from 70 to 120 cc. at rest; the minute output averaged 11.7 liters as compared with from 5 to 8 liters in normal persons at rest. The increased output of the heart may not be due to the tachycardia per se, for Stewart and Crawford [2] induced regular tachycardias by means of single induced break shocks thrown into the auricle at a regular rapid rate of between 250 and 400 per minute, and found that the blood flow was usually unchanged and in one third of the observations it was decreased.

Observations on the size of the heart in hyperthyroidism are difficult to obtain. Chvostek [3] stated that "only in severe cases of exophthalmic goiter is there hypertrophy of the heart." According to Bickel,[4] the pathologic anatomy of the heart in exophthalmic goiter consists essentially in an increase of the volume of the organ. Willius and Boothby [5] observed that the hearts of most patients with exophthalmic goiter or adenomatous goiter with hyperthyroidism were only moderately enlarged. In their series of cases the blood pressure was 147 systolic and 73 diastolic with a pulse rate of 123, and 153 systolic and 83 diastolic with a pulse rate of 110 in exophthalmic goiter and adenomatous goiter, respectively. Wilson [6] asserted that in hyperthy-

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* From the Department of Pathology of Northwestern University Medical School.

1. Wright, Samson: Applied Physiology, London, Oxford University Press, 1926, p. 128.

2. Stewart, H. J., and Crawford, J. H.: J. Clin. Investigation **3**:449, 1926.

3. Chvostek, F.: Wien. klin. Wchnschr. **30**:383 and 643, 1917.

4. Bickel, G.: Schweiz. med. Wchnschr. **11**:251, 1926.

5. Willius, F. A., and Boothby, W. M.: M. Clin. North America **7**:189, 1923.

6. Wilson, F. N.: Cardiac Disturbances Associated with Diseases of the Thyroid Gland, J. A. M. A. **82**:1754 (May 31) 1924.

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roidism "we find enlargement of the heart." Symmers [7] reported six cases of idiopathic cardiopathy—enlargement of the heart due to dilatation and hypertrophy of all of the chambers or of different combinations of the chambers—without valvular, pericardial, arterial, renal, pulmonary or other causes customarily invoked to explain enlargement of the heart. In all of these cases the thyroid showed chronic interstitial and hyperplastic thyroiditis.

The experimental work on this subject recorded in the literature appears to have been limited to rats and rabbits. Iscovesco [8] gave daily injections of thyroid extract and observed loss of body weight in old animals, together with hypertrophy of the various viscera. Hoskins,[9] working with white rats, observed "marked hypertrophy of the heart." He estimated that this increase in heart weight amounted to 24.6 and 16.7 per cent, respectively, in old and young female rats, and to 36 and 15.4 per cent, respectively, in corresponding males. Hewitt [10] found that the administration of 0.1 Gm. or more of fresh thyroid daily to adult male white rats caused hypertrophy of the heart. We have been unable to find in the literature any reference to the effect of thyroid feeding on the size of the heart in dogs. Cameron and Carmichael [11] fed thyroid preparations to young rats and rabbits and produced hypertrophy of the heart.

EXPERIMENTAL WORK

The experiments herein reported are concerned with eleven dogs, to ten of which 10 Gm. of desiccated thyroid (Armour and Company) was fed daily, and to the other dog, 20 Gm., for periods varying from thirty-two to one hundred days. In all of these animals the final body weight was recorded (designated as F.B.W. in the tables), and in ten, the original body weight was also recorded (designated as O.B.W. in the tables). After the animal had been killed the heart was carefully denuded of fat and weighed. It was then dissected according to Mueller's method,[12] and the auricles (designated as Au.W.), the ventricles and septum combined (designated as V.W.), the right ventricle (designated as R.V.W.), the left ventricle (designated as L.V.W.) and the septum were each weighed separately, and their respective

7. Symmers, D.: Cardiopathy and Goiter, Arch. Int. Med. **21**:337 (March) 1918.

8. Iscovesco, H.: Compt. rend. Soc. de biol. **76**:75, 1914.

9. Hoskins, E. R.: J. Exper. Zool. **21**:295, 1916.

10. Hewitt, J. A.: Quart. J. Exper. Physiol. **12**:347, 1918-1920.

11. Cameron, A. T., and Carmichael, J.: J. Biol. Chem. **45**:69, 1920; Tr. Roy. Soc., Canada **16**:57, 1922; ibid. **18**:105, 1924.

12. Mueller: Die Mässenverhältnisse des menschlichen Herzens, Braunschweig and Leipzig, 1883; cited by Hasenfeld: Deutsches Arch. f. klin. Med. **59**:193, 1897.

weights were recorded. Body weights and corresponding heart weights were recorded for thirty-one normal dogs kept under similar conditions and fed on the same diet as those to which desiccated thyroid was administered. In addition, records of body weights and whole heart weights have been collected from the literature in cases of experiments on inanition in dogs.[13] For comparison, the studies on changes in heart weights in animals in which aortic regurgitation had been induced by Stewart [14] and by Herrmann [15] were analyzed. The following ratios, with their designations in the tables, were analyzed and compared with corresponding ratios in inanition and aortic regurgitation:

H.W./N.B.W. = heart weight-body weight ratio in normal dogs.
H.W./O.B.W. = heart weight-original body weight ratio in thyrotoxic and starved dogs.
H.W./F.B.W. = heart weight-final body weight ratio in thyrotoxic and starved dogs.
L.V.W./N.B.W. = left ventricle weight-body weight ratio in normal dogs.
L.V.W./O.B.W. = left ventricle weight-original body weight ratio in thyrotoxic and aortic regurgitation dogs.
L.V.W./F.B.W. = left ventricle weight-final body weight ratio in thyrotoxic and aortic regurgitation dogs.
R.V.W./N.B.W.
R.V.W./O.B.W. = corresponding ratios for the right ventricle.
R.V.W./F.B.W.
Au.W./N.B.W.
Au.W./O.B.W. = corresponding ratios for the auricles.
Au.W./F.B.W.
V.W./N.B.W.
V.W./O.B.W. = corresponding ratios for the ventricles and septum.
V.W./F.B.W.

In table 1 it is seen that the mean heart weight-original body weight ratio of the thyrotoxic dogs was only 0.00058, while that of the starved dogs was 0.00171, less than the corresponding ratio for normal dogs. The mean heart weight-final body weight ratio for thyrotoxic dogs was 0.00232 greater, and that of the starved dogs 0.00059 greater, than the mean ratio of normal dogs. These figures become more significant when it is observed from table 1 that the mean loss of body weight in the thyrotoxic dogs was 31 and for the starved dogs 28.1 per cent. It is to be observed further that the mean losses of

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14. Stewart, H. A.: J. Exper. Med. **13**:187, 1911.

15. Herrmann, G. R.: Am. Heart J. **1**:213 and 485, 1925-1926.

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body weight in these two series of animals were almost the same—a difference of only 2.9 per cent—although the mean heart weight-body weight ratios were much lower in inanition.

In table 2, which is based on the figures in table 1, are shown the percentage differences between mean, minimum and maximum ratios in normal and in thyrotoxic and starved dogs. The figures for the latter group have been taken from papers published from Junkersdorf's

TABLE 1.—*The Mean Minimum and Maximum Heart Weight-Body Weight Ratios for Normal, Thyrotoxic and Starved Dogs*

Condition	Ratio	Mean	Minimum	Maximum	Mean Loss of Body Weight, Per Cent
Normal, own series	H.W./B.W.	0.00758	0.00660	0.00980	
Stewart	H.W./B.W.	0.00724	0.00599	0.00856	
Herrmann	H.W./B.W.	0.00708	0.00600	0.00994	
Thyrotoxicosis	H.W./O.B.W.	0.00700	0.00450	0.00825	
	H.W./F.B.W.	0.00990	0.00820	0.01190	—31.0
Inanition	H.W./O.B.W.	0.00587	0.00430	0.00708	
	H.W./F.B.W.	0.00817	0.00650	0.00900	—28.1

TABLE 2.—*The Percentage Difference Between Various Ratios in Normal, Thyrotoxic and Starved Dogs with the Corresponding Losses of Body Weight in the Latter Groups*

	Thyrotoxicosis		Inanition	
Ratios Compared	Percentage Difference	Percentage Loss of Body Weight	Percentage Difference	Percentage Loss of Body Weight
Mean H.W./N.B.W. Mean H.W./O.B.W.	— 7.7	—31.0	—22.5	—28.1
Mean H.W./N.B.W. Mean H.W./F.B.W.	+31.6	—31.0	+ 7.8	—28.1
Min. H.W./N.B.W. Min. H.W./O.B.W.	—18.6	—46.5	—21.3	—50.2
Min. H.W./N.B.W. Min. H.W./F.B.W.	+46.4	—46.5	+16.1	19.1
Max. H.W./N.B.W. Max. H.W./O.B.W.	—15.8	—30.4	—27.8	—20.7
Max. H.W./N.B.W. Max. H.W./F.B.W.	+21.4	—30.4	— 8.2	—43.5

laboratory.[18] In the column "percentage difference" in table 2, the figures indicate the degree to which the second ratio in each pair is greater or less than the first ratio in each pair. From this table three facts appear to be evident: 1. The mean, minimum and maximum heart weight-final body weight ratios in thyrotoxic dogs not only were much greater than the corresponding ratios in normal dogs, but were also considerably greater than the corresponding ratios in the starved animals. 2. The mean, minimum and maximum heart weight-original body weight ratios for thyrotoxic dogs were less than the corresponding ratios for normal dogs, but the difference was considerably less than

in the case of the starved dogs. 3. The minimum heart weight-original body weight and heart weight-final body weight ratios were found in the same animal of the thyrotoxic series, but in different dogs in the inanition series. The same applies to the maximum heart weight-original body weight and heart weight-final body weight ratios.

Using the normal ratio of 0.00758, the heart weight that would have been normal for the final body weight of each thyrotoxic dog was calculated. This figure was compared with the actual heart weight of the animal. In each instance the actual weight exceeded the calculated weight. It is seen from table 3 that if the figures in the last column were plotted as ordinates and the percentage loss of body weight as abscissae the curve would be remarkably regular. The maximum difference was in the animal that had lost 30.4 per cent of its body weight.

TABLE 3.—*The Percentage Difference Between the Actual Heart Weight and the Calculated Heart Weight for the Final Body Weight in Thyroid-Fed Dogs*

Dog No.	Days of Thyroid Feeding	Original Body Weight, Kg.	Final Body Weight, Kg.	Percentage Loss of Body Weight	Actual Heart Weight, Gm.	Calculated Heart Weight for Final Body Weight, Gm.	Percentage Difference Between Actual and Calculated Heart Weight
1	48	11.9	10.2	14.3	85.0	77.5	+ 8.85
2	49	14.5	11.35	21.7	95.0	86.0	+ 9.80
3	57	11.6	8.8	24.2	92.0	67.0	+27.0
4	93	14.6	10.25	29.8	110.5	77.5	+30.0
5	82	9.7	6.75	30.4	80.0	52.3	+35.0
6	22	11.9	8.04	33.5	89.0	61.0	+31.5
7	70	9.2	5.9	35.8	63.0	45.0	+28.5
8	57	10.5	6.7	36.1	71.0	51.0	+28.0
9	91	15.85	9.65	39.2	84.0	73.0	+13.0
10	100	13.9	7.39	46.5	60.5	56.0	+ 7.5

Mean percentage difference = + 21.

The highest part of the curve corresponds to the zone of from approximately 25 to 35 per cent loss of body weight. The difference between the actual and the calculated heart weights appears to be more directly related to the loss of body weight than to the length of time thyroid was fed to the animal.

Similar calculations were made for the heart weight that would have been normal for animals of the final body weight in a series of reports on inanition from Junkersdorf's laboratory,[13] and these were compared with the actual heart weights of the same animals. The percentage difference between the actual and the calculated heart weights in this series ranged from —16.3 in a dog that had lost 29.5 per cent of its body weight, to maxima of +15.5 in a dog that had lost 20.7 per cent and +15.8 in one that had lost 43.5 per cent. It is evident, therefore, that this percentage difference in the starved dogs has no such definite relation to the loss of body weight as in the thyrotoxic series. The mean percentage difference was more than four times as

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great in the thyrotoxic dogs as in the starved animals— + 21 and + 5, respectively.

It would appear from the foregoing data that an apparent increase in heart weight of from a mean value of approximately 5 to a maximum of approximately 16 per cent may be accounted for by the fact that the heart does not lose weight to the same extent as the body as a whole. Any such increase greater than 16 per cent is probably due to an actual increase in the size of the heart. If this is correct, those thyrotoxic dogs that had lost from approximately 25 to approximately 35 per cent (actually from 24.2 to 36.1 per cent) showed an actual hypertrophy of the heart. In the most marked case, that of dog 5 with 30.4 per cent loss of body weight, the actual increase in heart weight was more than 25 per cent (35 per cent minus the mean difference of 5 per cent due to failure of the heart to lose weight as rapidly as the

TABLE 4.—*Ratios Between Actual Weights of Different Parts of the Heart and the Body Weight in Thyrotoxic and Normal Dogs*

	Thyrotoxicosis			Normals		
Ratios	Mean	Minimum	Maximum	Mean	Minimum	Maximum
L.V.W./O.B.W.	0.00278	0.00218	0.00345	0.00293	0.00194	0.00392
L.V.W./F.B.W.	0.00415	0.00354	0.00465			
R.V.W./O.B.W.	0.00143	0.00072	0.00176	0.00161	0.00117	0.00237
R.V.W./F.B.W.	0.00215	0.00135	0.00306			
V.W./O.B.W.	0.00690	0.00383	0.00735	0.00654	0.00475	0.00872
V.W./F.B.W.	0.00880	0.00725	0.01065			
Au.W./O.B.W.	0.00077	0.00054	0.00105	0.00081	0.00055	0.00135
Au.W./F.B.W.	0.00112	0.00080	0.00159			
L.V.W./H.W.	0.4114	0.3450	0.5613	0.3891	0.3160	0.4380
R.V.W./H.W.	0.2125	0.1658	0.2452	0.2153	0.1640	0.2600
L.V.W./R.V.W.	2.15	1.54	3.40	2.03	1.48	2.57

body as a whole). With an increasing loss of body weight above 35 per cent the heart appears to lose what it has gained as a result of hypertrophy.

If the foregoing figures do indicate actual hypertrophy of the heart, it is important to determine whether the organ increases in size in all its parts or whether the hypertrophy is limited to one or more chambers. In table 4 are shown ratios between actual weights of different parts of the heart and the body weight in thyrotoxic and normal dogs.

From table 4 it appears that: 1. The mean, minimum and maximum ratios between the weights of various parts of the heart and the final body weight are considerably greater than the corresponding ratios in normal dogs. 2. The ratios between the weights of various parts of the heart and the original body weight are not nearly as great as the percentage loss of body weight and do not differ markedly from the corresponding normal ratios. This is shown to better advantage in table 5.

From table 5 it is seen that the mean, minimum and maximum left ventricle-final body weight ratios exceeded the corresponding normal ratios. The mean and maximum left ventricle-original body weight ratios were less than the normal but the difference was not as great as the loss of body weight. The minimum left ventricle-original body weight ratio was actually greater than the corresponding normal ratio. The mean right ventricle-final body weight ratio was one-third greater, and the right ventricle-original body weight ratio only one-eighth less, than the normal. The mean total ventricle and septum weight-final

TABLE 5.—*Percentage Difference Between Mean, Minimum and Maximum Ratios Between the Weights of Various Parts of the Heart and the Original and Final Body Weights*

Ratios Compared	Percentage Difference	Percentage Loss of Body Weight
L.V.W./N.B.W. Mean L.V.W./O.B.W. Mean	— 5.12	—31.0
L.V.W./N.B.W. Mean L.V.W./F.B.W. Mean	+41.64	—31.0
L.V.W./N.B.W. Min. L.V.W./O.B.W. Min.	+12.37	—39.2
L.V.W./N.B.W. Min. L.V.W./F.B.W. Min.	+46.00	—21.7
L.V.W./N.B.W. Max. L.V.W./O.B.W. Max.	—12.00	—24.2
L.V.W./N.B.W. Max. L.V.W./F.B.W. Max.	+18.62	—35.8
R.V.W./N.B.W. Mean R.V.W./O.B.W. Mean	— 12.58	—31.0
R.V.W./N.B.W. Mean R.V.W./F.B.W. Mean	+33.60	—31.0
V.W./N.B.W. Mean V.W./O.B.W. Mean	— 9.0	—31.0
V.W./N.B.W. Mean V.W./F.B.W. Mean	+34.55	—31.0
Au.W./N.B.W. Mean Au.W./O.B.W. Mean	— 5.32	—31.0
Au.W./N.B.W. Mean Au.W./F.B.W. Mean	+38.27	—31.0

body weight and the mean auricle weight-final body weight ratios were approximately one-third greater than normal. The corresponding original body weight ratios were less than 10 per cent below the normal. These figures appear to indicate, therefore, that in the experiments here recorded feeding thyroid to dogs causes, especially in animals that have lost from 25 to 35 per cent of their body weight, an actual hypertrophy of the heart involving all of the chambers. This is brought out even more clearly when the figures in these thyrotoxic dogs are compared with corresponding figures obtained by Stewart and by Herrmann in experimental aortic regurgitation. This is shown in table 6.

Table 6 shows that the difference between the mean heart weight-final body weight ratio in thyrotoxic dogs and the heart weight-body

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weight ratio in normal dogs is almost as great as in aortic regurgitation, while in inanition the difference is much less. The mean left ventricle-heart weight ratio in thyrotoxicosis is only slightly less than in aortic regurgitation. The mean right ventricle weight-heart weight ratio is markedly less (20.5 per cent) in aortic regurgitation and is only 1.33 per cent less in thyrotoxicosis than the normal ratio. The left ventricle weight-right ventricle weight ratio is greatly increased in aortic regurgitation and only slightly increased in thyrotoxicosis. These figures indicate that the increase in size of the heart in thyrotoxicosis involves all of the chambers in contrast to aortic regurgitation in which the hypertrophy is practically limited to the left ventricle. In this connection, it is interesting to note that electrocardiograms of these thyrotoxic dogs showed no ventricular preponderance.

TABLE 6.—*Comparison Between Various Heart Weight-Body Weight Ratios in Aortic Regurgitation, Thyrotoxicosis and Inanition*

Percentage Difference Between Mean	Aortic Regurgitation, Per Cent		Thyrotoxicosis, Per Cent	Inanition, Per Cent
	Stewart	Herrmann		
H.W./N.B.W. H.W./F.B.W.	+39.5	+31.95	+30.61	+11.87
L.V.W./N.H.W. L.V.W./H.W.	+ 9.66		+ 5.73	
R.V.W./N.H.W. R.V.W./H.W.	—20.50		— 1.33	
L.V.W./R.V.W. Normal L.V.W./R.V.W.	+41.97	+31.00	+ 5.90	

In order to determine whether there was any reciprocal relationship between body weights and heart weights, correlation coefficients were calculated in the case of our normal and thyrotoxic dogs. These have been compared with the coefficients published by Herrmann. From the data published in Stewart's paper we have determined correlation coefficients in his normal animals and those in which he had induced experimental aortic regurgitation. A similar calculation was made from data in papers from Junkersdorf's laboratory in the case of dogs that had been starved for varying intervals of time. A correlation coefficient of 1 indicates that there is a perfect reciprocal relation between the weights compared. From table 7 it is seen that there is a definite correlation between body weight and heart weight in normal animals. The coefficient of correlation between heart weight and final body weight in inanition was only slightly less than the average normal, which indicates that in this condition the heart loses weight in almost the same proportion as the body as a whole. In the case of the thyrotoxic dogs the coefficient was, in every instance, considerably less than

the normal, which is evidence that in experimental hyperthyroidism the heart does not lose weight to the same extent as the body. This furnishes further indication that in the animals used in these experiments an actual hypertrophy of the heart did occur. In all except one instance the correlation coefficients were higher in thyrotoxicosis than in aortic regurgitation. This is in harmony with facts presented in other tables in this paper and shows that the hypertrophy in experimental thyrotoxicosis is not as great as in aortic regurgitation.

The coefficient of correlation between heart weight and right and left ventricle weights, respectively, is not as perfect as one would

TABLE 7.—*Correlation Coefficients*

Variables Correlated		Correlation Coefficients			
		Normals	Thyrotoxicosis	Inanition	Aortic Regurgitation
H.W. and F.B.W.	Own series	0.9062	0.8206	0.9075*	
	Stewart	0.9490			0.7670
	Herrmann	0.9152			
	Average	0.9235			
L.V.W. and F.B.W.	Own series	0.8790	0.8360		
	Stewart	0.9490			0.6795
	Herrmann	0.5104			
	Average	0.9128			
R.V.W. and F.B.W.	Own series	0.8104	0.7090		
	Stewart	0.8770			0.6893
	Average	0.8437			
H.W. and L.V.W.	Own series	0.9730	0.8967		
	Stewart	0.8900			0.8010
	Average	0.9315			
H.W. and R.V.W.	Own series	0.9675	0.8570		
	Stewart	0.9124			0.9040
	Average	0.9399			
H.W. and Au.W.	Own series	0.9038	0.7220		
	Stewart	0.962			0.7212
	Average	0.9329			
R.V.W. and L.V.W.	Own series	0.9200	0.7670		
	Stewart	0.8860			0.7000
	Herrmann	0.9688			
	Average	0.9239			

* Based on data published from Junkersdorf laboratory.

expect if all of the heart chambers were equally hypertrophied in thyrotoxicosis. In table 6 it was found that the mean left ventricle weight-right ventricle weight ratio was approximately 6 per cent greater than the corresponding normal ratio. The figures in table 4 show an almost identical difference. This suggests that the left ventricle was slightly more hypertrophied than the right. In order to determine this more accurately, the right and left ventricle weights that would have been normal for the heart weights in the thyrotoxic dogs and in Stewart's animals with aortic regurgitation were calculated (using the mean ratios 0.3891 and 0.2153 in table 4) and compared with the actual heart weights. It was found that the mean actual left ventricle weight in the thyrotoxic dogs was 6.9 per cent greater than the mean calculated weight, while the mean actual right ventricle weight was 2.25 per

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cent less than the corresponding calculated weight. In Stewart's dogs with aortic regurgitation the actual left ventricle weight was 17.3 per cent greater, and the actual right ventricle 17.8 per cent less, than the corresponding calculated weights. These figures seem, therefore, to indicate that in experimental hyperthyroidism the heart hypertrophies as a whole with a slightly greater increase (approximately 6 per cent) in the left ventricle. This is in striking contrast to aortic regurgitation in which the left ventricle is markedly increased.

SUMMARY

1. Feeding 10 Gm. of desiccated thyroid daily to healthy dogs can cause an actual hypertrophy of the heart.

2. This hypertrophy is related to the loss of body weight, and occurs in those animals which have lost from approximately 25 to 35 per cent of their original body weight. When the loss of weight exceeds approximately 35 per cent, the heart loses the weight it has gained in hypertrophy and the heart weight-final body weight ratio approaches that seen in simple inanition.

3. This hypertrophy involves all of the chambers of the heart with a slightly greater proportional increase in the left ventricle.

BILATERAL ABSENCE OF PULSE IN THE ARMS AND NECK IN AORTIC ANEURYSM *

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DETROIT

The absence of pulsation in the radial, brachial and carotid arteries of both sides is a rare condition. A patient showing such abnormality was under observation in the wards of the University Hospital. In a study of the literature only three reports of instances in which this striking abnormality occurred were found. We are collecting and reviewing these, adding our report of a case as a fourth.

INCIDENCE

Because of the frequency of aortic aneurysm, large groups of statistics are available dealing with signs and symptoms in the presence of this lesion. Boyd [1] in 1924 studied collected reports on 4,000 cases of thoracic aortic aneurysm, stating that over 5,000 cases had been reported in the literature. Since we are dealing with a not uncommon lesion, the finding of only three reports of cases of bilateral absence of pulse indicates the extreme rarity of this remarkable abnormality.

Pulse abnormalities, such as inequality and asynchronism and the less common unilateral absence of pulsation, are not infrequently discussed in the literature. Inequality in the size of the pulse wave in two similar arteries is probably the most frequent abnormal observation. Asynchronism of the pulse wave is also not infrequent. Unilateral absence of pulsation has been reported as occurring most often in the radial arteries, but it has been known to occur in the carotid, brachial and radial arteries of one side.

Hare and Holder [2] analyzed the observations in 953 cases of thoracic aneurysm and called attention to the abnormalities of the pulse. Of this number, 570 were cases in which the aneurysm was of the ascending portion of the arch, and pulse abnormality occurred in 13 of these.

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* From the Department of Internal Medicine, University of Michigan, Ann Arbor, Mich.

1. Boyd, L. J.: A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta, Am. J. M. Sc. **168**:654 (Nov.) 1924.

2. Hare, H. A., and Holder, C. H.: Some Facts in Regard to Aneurysm of the Aorta, Am. J. M. Sc. **118**:399 (Oct.) 1899.

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In 8, the right radial pulse was greater than the left; in 4, the left was greater than the right, and in 1, the pulse was absent in the left axillary, brachial, radial and carotid arteries. Aneurysm of the transverse arch occurred 104 times in the total group. Here pulse abnormality was noted 15 times, the left radial pulse being absent in 2, and the left being weaker than the right radial pulse in the remaining 13. In 110 cases of aneurysm of the descending portion of the aortic arch, the pulse was observed to be absent in the left radial artery in 2, and weaker than the right in 2 other instances. In the total number of reports of these cases there was no mention of bilateral absence of pulsation.

Pulse abnormalities have been recognized by careful observers of the last century as illustrated in the treatises by Corvisart,[3] Bertin,[4] Flint [5] and Fuller.[6] However, these astute clinicians have left no record of the absence of arterial pulsation occurring bilaterally. In the literature of the past two decades, such as the papers by Findlay,[7] Arnold,[8] Kahn [9] and others, time and space have been given to pulse inequalities, but no mention has been made of the remarkable observation under discussion in this paper. This also applies to the complete modern textbooks, such as those by Strümpell,[10] Külbs,[11] Hirschfelder,[12] Dieulafoy [13] and the modern American Systems of Medicine.[14]

Thus we see that in the literature of the last century and a quarter, dealing with the signs in aneurysm, unilateral pulse abnormality is commonly recognized, but there has been a universal lack of discussion of absence of arterial pulsation on both sides. There is only one

3. Corvisart, J. N.: Essay on Organic Diseases and Lesions of the Heart and Great Vessels (Trans.), Philadelphia, 1812.

4. Bertin: Treatise on Diseases of the Heart and Great Vessels, Philadelphia, 1833.

5. Flint, Austin: A Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart, Philadelphia, 1859.

6. Fuller, H. W.: Diseases of the Heart and Great Vessels, London, 1863.

7. Findlay, L.: On Delay or Retardation of the Pulse as a Sign of Aneurysm, Practitioner **83**:803 (Dec.) 1909.

8. Arnold, H. D.: Importance of the Early Detection of Aneurysm of the Aorta, Am. J. M. Sc. **135**:515 (April) 1908.

9. Kahn, M. H.: Pulse Difference in Aneurysm of the Arch of the Aorta, M. Clin. North America **8**:347 (July) 1924.

10. Strümpell, A.: Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten, Leipzig, 1928, vol. 1, 578.

11. Külbs, F.: Handbuch der inneren Medizin, Berlin, 1928, vol. 2, p. 1, 476.

12. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Philadelphia, 1913.

13. Dieulafoy, G.: Textbook of Medicine, New York, 1914, vol. 1, p. 512.

14. Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1924; Oxford Medicine, New York, Oxford University Press, 1928; Nelson's Loose-Leaf Living Medicine, New York, T. Nelson & Sons, 1920.

exception to this. Osler [15] mentioned that it has been reported that there has been complete absence of the pulse in the arteries of the head and upper extremities in large aneurysm of the transverse arch. (Incidentally, he reported an instance of obliteration of the pulse in the abdominal aorta and in both lower extremities in the presence of aneurysm of the abdominal aorta.)

Three isolated reports are available in the literature, of cases in which there was obliteration of the pulse in the arteries of the upper extremities. In two of these there was also lack of pulsation in the arteries of the neck. These reports of cases are reviewed below and we have added our report of a case as a fourth.

CASE REPORTS

The first case is one reported by Broadbent,[16] before the Clinical Society of London in 1875.

A laborer, aged 50, was admitted to the hospital because of ascites and chronic bronchitis with emphysema. He had been a sailor and had had syphilis. The ascites was presumed to have as a basis hepatic cirrhosis, and during the seven months before his death paracentesis was done frequently.

Of particular interest was the circulation of the upper extremities, and we shall quote this description. "There was no pulse at either wrist, but while this was the case, the radial arteries could be distinctly felt full of blood and could be rolled under the finger. That this cord-like object under the fingers was really the radial artery was shown by the fact that when the arm was raised the blood receded, and the artery collapsed and became imperceptible. It should be added also, that from time to time, a faint flickering pulsation could be detected, more frequently and more perceptibly in the left than the right radial. The flow of the blood through the veins of the back of the hand and forearm was vigorous, and the hands were warm and presented no appearance of languid or deficient circulation. The muscular condition of the extremities was good. An additional interest was imparted to the condition by the statement of the patient that the absence of pulse had been detected (had come on as he said) after he had been thrown from a train in Boxmoor tunnel thirty years before. On further investigation, pulsation was found to be absent in the brachial and subclavian arteries; present in the left carotid, and feebly in the right; vigorous in the femorals and posterior tibials."

Examination demonstrated no abnormality of the heart, no abnormal pulsation and no dulness in the upper part of the chest. In other words, Broadbent said, there was no evidence for the diagnosis of aneurysm or intrathoracic tumor.

Broadbent was frankly puzzled by the observations and kept the patient under observation until his death. At necropsy, the heart was essentially normal. The aorta was slightly enlarged; otherwise it appeared unaltered. When it was opened, there was found little disease of the internal coat, and the wall was elastic. To quote: "It was seen, however, that the orifices of the innominate and the left

15. Osler, William: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 864.

16. Broadbent, W. H.: Absence of Pulsation in Both Radial Arteries the Vessels Being Full of Blood, Tr. Clinical Society, London, 1875.

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carotid arteries were close together, and the mouth of the former was exceedingly small. The innominate was found not only to be narrowed at its origin, but rigid. An atheromatous patch surrounded the mouth of the vessel involving the structures both of the aorta and the innominate; it was hard and brittle and separated easily from the outer tunic. Immediately above its origin, the innominate enlarged to its usual size, and possessed its normal elasticity. Here, then, was the explanation of the absence of the pulse with a full vessel at the right wrist. It was found that the left vertebral artery, instead of arising from the subclavian, sprang from the aortic arch close to the origin of the subclavian, the orifice of which was narrowed to the size of a crow quill by the proximity of the vertebral. Here again atheroma had invaded the constricted orifice and rendered it rigid, while the artery beyond was healthy and of full diameter. The absence of pulsation in the two radials instead of being due to a single lesion, was thus caused by a repetition of a precisely similar condition at two separate points."

Comment.—Broadbent's report is the first in which bilateral absence of the pulse in the upper extremities is described. He was at a loss satisfactorily to explain his observations as indicated in the following sentence: "I was unable to frame, or to obtain from physicians who saw the patient, any explanation of the phenomenon described, or to find recorded cases throwing light upon them." In this case, we are not dealing with aneurysm as the basis for the obliteration of pulsation. According to the history, the patient had had syphilis, and a unilateral absence of pulse was alleged to have been present thirty years before. The pathologic observations explained the phenomenon, the atheroma accentuating and complicating a congenital anomaly in the origin of the vessels arising from the aortic arch.

The second case is that reported by Crawford [17] in 1921, in which he found absence of arterial pulsation in both upper extremities and the neck, in the presence of thoracic aneurysm.

History.—A white man, aged 52, complained of severe occipital headache, pain in the back of the neck and shortness of breath. These symptoms had been of eighteen months' duration. The headache had been a constant feature, and dizziness and a tingling sensation in the left thumb had been present for twelve months. Six weeks before admission, during a "weak spell," the patient's wife had been unable to obtain the pulse. The patient said that he had had gonorrhea but not syphilis.

Examination.—The skin of the face and neck was dusky, and there was slight cyanosis of the lips and ears. The pupils were unequal, but pupillary reflexes were prompt. The superficial veins of the face, neck and chest were visible; those of the forearm were prominent. The radial and brachial arteries were palpable and compressible, but no pulsation was present in the vessels now in the carotids. The apex rate was 120 per minute. A diffuse slightly expansive pulsation was present in the upper two or three intercostal interspaces, more pronounced to the right of the sternum. Tracheal tug was present. The heart sounds were normal at the apex. A soft systolic murmur with a muffled second sound was heard at the second and third interspaces on either side of the sternum.

17. Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, J. A. M. A. **76**:1395 (May 21) 1921.

No abnormality of pulsation was noted in the abdomen or lower extremities. The blood pressure in the lower extremities was 125 systolic.

A diagnosis of aneurysm was made and this was verified by fluoroscopic examination. The greater part of the arch and descending thoracic aorta was found to be involved. The blood gave a positive Wassermann reaction.

Comment.—In this patient there was found to be complete obliteration of the pulse in the radial, brachial and carotid arteries of both sides. This was apparently the condition six weeks earlier when the patient's wife, a trained nurse, failed to obtain the pulse. A diagnosis of aneurysm was verified roentgenologically, and the patient had a positive serologic reaction for syphilis. We wish to call attention particularly to the symptoms presented. Some of these were probably on a cardiac basis, but it should be emphasized that the patient had complained of constant headache for eighteen months, and dizziness for a year.

The third case is that reported by Shikhare [18] in 1921.

A middle-aged man, a carpenter, entered the hospital because of attacks of dizziness. In the history, it was noted that the patient was subject to attacks of dizziness sometimes ending in syncope. During such attacks, he usually uttered a cry, and bending forward, would fall to the ground. Profuse perspiration accompanied the attacks.

Examination.—The patient was poorly nourished. He could hardly walk unsupported. There was marked intolerance to light, and ophthalmoscopic examination showed some patches of choroiditis. The outstanding observation was the absence of pulsation of all arteries of the upper half of the body. The arteries could be felt in their normal sites and, being somewhat rigid, could be rolled under the finger. The pulsation in the abdominal aorta and in the arteries of the lower extremities was normal. Cardiac examination was negative.

Necropsy.—The ascending aorta and the arch showed a fusiform aneurysmal dilatation which was occupied by a large antemortem clot obliterating almost the whole of its lumen. This large central clot sent projections into and almost obliterated the lumen of the innominate artery and its branches, the right common carotid and right subclavian, and also into the corresponding arteries of the left side to a variable extent. These finger-like projections acted as loosely fitting plugs for the different arteries mentioned, allowing a certain amount of blood to pass. There was a passage between the posterior surface of the central clot and the posterior aortic wall which probably allowed a fair amount of blood to pass to the descending aorta.

Comment.—In this patient also, in whom there was a bilateral lack of pulse wave in the arteries of the upper extremities and neck, the aortic lesion present was that of aneurysm. The anatomic observation of a large clot in the aneurysmal sac is of great interest. Though the trunk vessels arising from the aortic arch were almost completely obstructed by projections of the clot into them, enough blood apparently

18. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, Indian J. Med. **2**:326 (March) 1921.

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passed so that nutrition of tissues was maintained. However, the obstruction prevented transmission of the pulse wave to the column of blood in the affected vessels.

Although the history is meager, we again wish to call attention to the major symptom. Frequent attacks of dizziness going on to syncope brought the patient for medical attention.

The fourth case is that which prompted the collection of this series of reports. This patient was observed by us for a short time in the wards of the University Hospital.

F. K., an Austrian factory laborer, aged 35, entered the University Hospital in October, 1928, complaining of dizziness and fainting attacks.

History.—Seven weeks before admission to the hospital, the patient suddenly became dizzy and nauseated while at work. Everything became black before his eyes, and he fell to the floor unconscious. He was unconscious only a few seconds and recovered when his fellow workmen lifted him to his feet. For three weeks, the patient was troubled daily with dizzy attacks in which he would have to support himself to keep from falling. At times he did fall unconscious. At the end of this period, he went to bed and remained there until his admission to the hospital. During the period spent in bed, he was dizzy only when getting up, and on one such occasion fell unconscious. At times, vision was poor in that everything appeared dark, but at such times he was neither dizzy nor nauseated.

For six years, the patient had had pain over the front of the chest, the pain being dull and lasting only a few moments. During the past seven weeks, the pains had been more frequent and more severe, occurring either over the right or the left side of the chest in front.

Appendectomy was done four years before, and two years later laparotomy was necessary for acute intestinal obstruction. The patient stated that on that admission to the hospital the left pulse at the wrist could not be obtained. Of importance is the history of a primary genital lesion in 1917. There had been a loss of 30 pounds (13.6 Kg.) in the past two years.

The patient was married, but the wife had never been pregnant.

Physical Examination.—The patient was a well developed man, apparently comfortable in bed either lying down or sitting up. The head was normal. The pupils were round and equal and reacted promptly to light and in accommodation. The nose, mouth and throat were normal. There was no huskiness of the voice. The larynx appeared normal. A slight but definite tracheal tug was present.

The chest appeared to be symmetrical, but there was lagging and decreased expansion of the left side on inspiration. Respirations were normal. There was a diffuse heaving impulse over the whole upper part of the chest, more marked over the left upper part of the chest and precordium. This was synchronous with the heart beat. Retromanubrial dulness was increased to both sides in the first and second interspaces, especially to the left. The cardiac apex impulse was visible in the fifth interspace 10 cm. from the midsternal line. On auscultation there was noted some tachycardia, but rhythm was regular. The heart sounds were of fair quality. The second sound at the base was ringing in character. To the right of the sternum in the second intercostal space and extending to the right infraclavicular region were heard a high pitched blowing systolic murmur and a lower pitched short diastolic murmur.

The radial and brachial arteries could be palpated, and were full, but no pulse was present. The absence of pulsation was noted also over the carotid arteries

and their superficial branches. The pulsation of the abdominal aorta was normal, and arteries of the lower extremities showed a normal pulse down to and including the dorsalis pedis. The upper extremities showed no evidence of impaired circulation, being of normal color, warm and with normal mobility. There was rapid return of color following pressure on skin or nail beds. No clubbing of the fingers was present nor incurvature of the nails. The blood pressure as obtained in the lower extremities was 178 systolic with 110 diastolic.

There was no evidence of venous stasis in the arms or upper part of the chest as might be expected in mediastinal pressure. No abnormal pulsations could be made out over the anterior surface of the chest which would indicate a collateral circulation. Posteriorly, at the angle of the left scapula in the eighth interspace was a visible and palpable pulsation, demonstrable only over a length of about 2 cm. This was synchronous with systole. There was no comparable pulsation on the opposite side.

The remainder of the physical examination was negative, except for a generalized lymphadenopathy including the cervical, axillary, epitrochlear and inguinal glands. The spine was normal, except for a slight dorsal kyphoscoliosis. Reflexes were normal.

Technical Examinations.—Examinations of the urine and stools yielded negative results on all occasions. The blood showed a hemoglobin content of 85 per cent, a red cell count of 4,600,000 and a white cell count of 9,700 with a normal blood smear. The Kahn test was 4 plus. The roentgenologist reported a wide mediastinal pulsating shadow bulging to the left, and made a diagnosis of aneurysm of the ascending and transverse portions of the aortic arch. An electrocardiogram showed only sinus tachycardia.

Comment.—In this patient, in whose case a diagnosis of aortic aneurysm was substantiated by roentgenologic examination, there was obliteration of the pulse in the arteries of the upper extremities and of both sides of the neck. Of interest is the fact that an area of pulsation was present in the region of the angle of the left scapula. Again we wish to emphaize that the symptom which brought the patient to the hospital was dizziness occurring in attacks leading, at times, to unconsciousness.

EXPLANATION OF ABSENCE OF PULSATION

Several explanations have been advanced for the phenomena of pulse inequality or absence of pulse in the arteries of the upper portion of the body. Though the available discussions on this phase of the subject have, almost without exception, dealt merely with pulse inequality or at most with unilateral absence of pulse, the explanations offered may be carried over into a discussion of the bilateral obliteration of arterial pulsation.

The most universal explanation offered for unilateral absence of pulsation has been on the basis of hydrodynamics, in that a large distensible sac may so absorb the force of the cardiac systole that an intermittent stream is converted into a continuous one. Osler [15] quoted Harvey to this effect, and experimental work by Marey [13] bore

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out this supposition. Kahn [9] advanced this explanation as one of several for pulse obliteration.

A second explanation offered for abnormality in the pulse is that of thrombus formation within the aneurysmal sac. Kahn [9] and Dieulafoy [13] agreed that such a thrombus may partially obstruct the orifice of an arterial trunk arising from the sac. Such encroachment on the opening of an artery would diminish the flow of blood into it and as a result the pulsation usually transmitted would be lost. In Shikhare's case, an advanced degree of such a condition was demonstrated in that projections from the large main thrombus fitted as loose plugs into the arteries arising from the sac.

Another explanation offered by authors, such as Flint,[5] Kahn,[9] Strümpell [10] and Sansom,[19] is that an artery leading from the aorta may be obliterated to some degree by pressure on it by the aneurysmal sac. Flint [5] stated specifically that the aneurysmal tumor may press on the subclavian, carotid or innominate artery. In such case, the pulse abnormality is merely one of several possible pressure phenomena. Though no certain conclusions can be drawn from Crawford's case, the physical observations as described for his patient suggest pressure as a possible cause for pulse obliteration. It may be pointed out that he described duskiness and cyanosis of the face and lips, and inequality of the pupils, and said that the superficial veins of the face and upper part of the chest were visible, those of the forearm being prominent. These details are suggestive of pressure in the mediastinum.

Narrowing or distortion of the orifice of one or more of the arteries arising from the aorta may explain pulse abnormalities. Strümpell [10] said that this may occur in arterial trunks arising from an aneurysmal sac. Osler [15] maintained that pulse inequality is most frequently on this basis in the presence of aneurysm. That atheroma at an arterial orifice may play a part is accepted by Dieulafoy.[13] Although Broadbent's case is not one of aneurysm, the pulse obliteration was due to such circumstances. He said that as a result of the atheroma the arteries were cut off from the general expansive movement of the aorta, and that a small stream, insufficient to distend the peripheral arteries, was allowed to pass.

Since congenital variation in the origin of the arterial trunks from the aortic arch is not rare, it is conceivable that such an anomaly might occur coincident with such a common lesion as aneurysm. In such an event, owing to fewer trunk arteries, the possibility of bilateral absence of pulse would be enhanced. In the case of Broadbent's patient, there was an anomalous pattern in the arteries springing from the aortic arch.

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19. Sansom, A. E.: Twentieth Century Practice of Medicine, New York, 1895, vol. 4, p. 505.

Because narrowing of an orifice by local changes, or obstruction by a thrombus can occur, it is possible that such a process might slowly progress until complete obliteration of the trunk artery is produced. In such an event, a collateral circulation would needs take up the burden of supplying blood to the parts cut off from their normal supply. In case of bilateral obliteration of the pulse, the complete obstruction with collateral circulation would not need to be bilateral. In fact, it might more probably be unilateral owing to either a more extensive or a more prolonged involvement on one side. In our patient, such a possibility may be considered. The pulsation at the angle of the left scapula undoubtedly was produced by the intercostal artery and so suggests a collateral circulation in which the intercostal arteries were involved. Obliteration at the orifice of the left subclavian due to whatever cause might well lead to a collateral circulation involving the intercostal and the internal mammary arteries. From this point of view, it is of interest that two years before, the left radial pulse was absent. Thus the etiologic factor, whether thrombus or local change at the orifice, may have involved the left subclavian first or more extensively than the innominate, or left carotid, and later may have led to complete obliteration with a resultant collateral circulation on that side. Complete obstruction at the origin of the subclavian by pressure from the aneurysmal sac is not probable in the absence of other pressure phenomena.

COMMENT

Because of the rarity of the remarkable condition under discussion in this paper, it was thought to be of sufficient interest to collect the three available reports from the literature and review these with our case. Inequality of pulses or unilateral absence of pulsation is not infrequent.

Syphilis presumably was the etiologic factor in the aortic lesion in each of the collected cases. In Broadbent's case there was a history of syphilis, and pathologically lesions were present in the aorta at the orifices of the arterial trunks. Such changes in a man of 50 years, with a history indicating pulse abnormality for many years make syphilis most probable. In Crawford's case, and in our case, the diagnosis of aneurysm was verified roentgenologically, and in each there was serologic evidence of syphilis. Shikhare gave no serologic data, but the observation at necropsy of aortic aneurysm in a middle-aged man is presumptive evidence of syphilis.

We believe it to be important to direct attention to the symptoms which caused the patients to seek medical attention. In the three patients suffering from aneurysm, the complaints were almost identical and indicate deficient blood supply to the brain. Occipital headaches, dizziness, syncope, nausea and visual impairment constituted this group

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of symptoms. Broadbent dwelt on other features of the history in his patient and failed to mention similar symptoms.

From a physical standpoint, there was absence of arterial pulsation in the neck and upper extremities in all the collected cases, with the exception of a weak carotid pulse on one side in Broadbent's patient. In one subject, some signs in the examination indicated possible pressure phenomena. Otherwise, the parts supplied by the pulseless arteries failed to demonstrate any physical evidence of deficient circulation. In all, the parts were warm, of normal nutrition and of good color. In our patient there was a rapid return of color after the release of pressure on the skin or nail bed.

The varied explanations of pulse inequality and unilateral absence of pulsation which have been advanced from time to time have been considered and applied to the lack of the pulse bilaterally. We have discussed the possibility of complete obliteration of an arterial trunk with a resultant collateral circulation. The history and examination in our patient presented data warranting the consideration of this possibility.

SUMMARY AND CONCLUSIONS

1. Three available case reports of the bilateral absence of pulse in the radial, brachial and carotid arteries have been collected from the literature. We have added a fourth.

2. Though pulse inequality and unilateral absence of pulse are not infrequently mentioned in the literature, the obliteration of the pulse bilaterally undoubtedly is rare, since practically no reference is made to it in the many discussions on signs in aneurysm.

3. Syphilis was unquestionably present in the four collected cases; in three there was aneurysm of the aorta.

4. The accepted explanations for pulse inequality in the presence of aneurysm may be applied in the condition under discussion.

5. It is possible that a process causing partial obstruction to an arterial orifice may lead to complete occlusion with a resultant collateral circulation.

6. From the histories as given in the case reports, it may be concluded that in like instances symptoms resulting from deficient cerebral blood supply will probably cause the patient to seek medical advice. Attacks of dizziness leading to syncope were the most striking symptom in each of the patients suffering from aneurysm with absence of arterial pulse in the neck and upper extremities.

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ABDOMINAL EXPLORATION IN CASES DIAGNOSED CHOLECYSTITIS OR CHOLELITHIASIS BEFORE OPERATION *

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In a previous paper we [1] reported the results of abdominal exploration undertaken during operation for gastric or duodenal ulcer. A large variety of pathologic conditions, which had escaped detection preoperatively, were detected during laparotomy. Some of these conditions were merely of academic interest and probably were not productive of significant symptoms. Others were sufficiently masked by symptoms related to the disease of major importance to escape detection. Some were of definite clinical importance and should have been recognized preoperatively.

In reviewing the records of a large number of patients who had undergone cholecystectomy for cholecystitis or cholelithiasis, we became impressed by the large variety of associated diseases which were found. We believed that it might be of some interest (1) to tabulate the diseases most frequently found associated with cholecystitis or cholelithiasis; (2) to ascertain which diseases most frequently mask themselves in the syndrome of disease of the gallbladder and thus escape preoperative comment, endeavoring to determine whether, by any signs, the presence of these diseases should have been suspected by the examining clinician or surgeon, and (3) to focus our attention especially on the more important rare complications, thus gathering information which might help us in detecting them.

The records of 879 patients were studied. In selecting these records, we had the advantage not only of the surgeon's judgment in regard to his observations but of the opinions expressed by the pathologists who studied the removed specimens.

In all of the cases, pathologic conditions in the gallbladder were sufficient to warrant its removal. In many instances, unusual complications were discovered only after the minutest study of the removed tissues.

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* From the Division of Medicine, the Mayo Clinic.

1. Hartman, H. R., and Rivers, A. B.: Benign Gastric and Duodenal Ulcer: The Clinical Diagnosis and the Conditions Found at Operation, Arch. Int. Med. 44:314 (Sept.) 1929.

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A prerequisite to the acceptance of these records for study was that they include only a single relevant preoperative diagnosis, such as cholelithiasis. Thus, for instance, cases in which the diagnosis was cholecystitis or duodenal ulcer were not included. Cases in which there was a dual diagnosis of independent conditions, such as cholecystitis and mature cataract of the left eye, were not rejected for study because obviously such irrelevant conditions could scarcely affect the preopera-

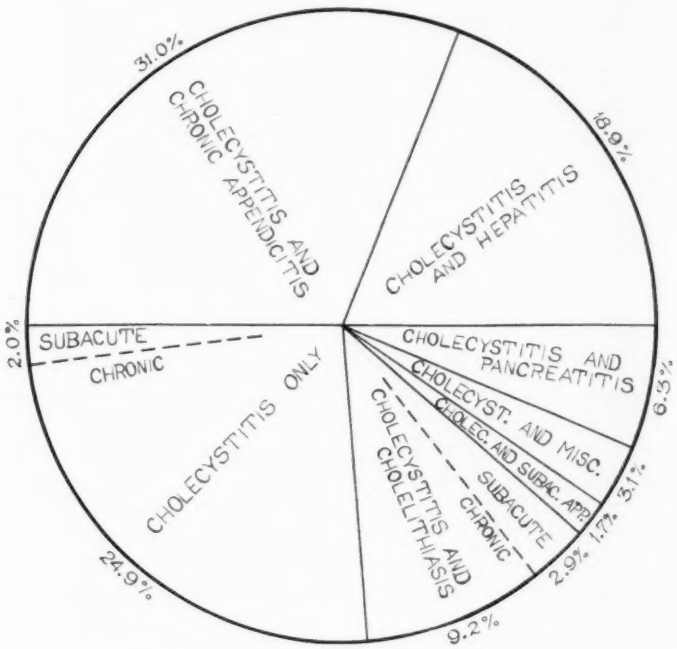

Chart 1.—Conditions found at operation in 287 cases in which the preoperative diagnosis was of cholecystitis only: *Misc.* indicates miscellaneous conditions as follows: duodenal ulcer, four cases; duodenitis, one case; cholangeitis, one case; accessory lobes of the liver, one case; myoma of the anterior wall of the stomach, one case; Lane's kink, one case, and cholecystoduodenal fistula, one case; *subac. ap.* indicates subacute appendicitis.

tive clinical history. In 287 of these cases, the preoperative diagnosis was cholecystitis, and in 592 operation was undertaken on the diagnosis of cholelithiasis.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS CHOLECYSTITIS ONLY

Cases in which the preoperative diagnosis was cholecystitis were studied separately. The complications have been listed diagrammatically

so that the frequency, in percentage, of each complication becomes readily apparent. In chart 1, we have represented diagrammatically the diverse pathologic entities encountered during operations which were performed after a preoperative diagnosis of cholecystitis had been made; these preoperative diagnoses did not include any mention of cholelithiasis. In these cases, the diagnosis of chronic cholecystitis was corroborated at operation, but in 71 per cent of the cases some additional condition, either of the gallbladder or of other organs, and not specifically mentioned preoperatively, was discovered. In 2 per cent of the cases, subacute cholecystitis was found uncomplicated by any other pathologic condition. Thirty-one per cent of these cases were complicated by chronic appendicitis; 1.7 per cent by subacute appendicitis; 18.9 per cent by associated hepatitis, and 6.3 per cent by pancreatitis. In 12.1 per cent of these cases, gallstones were found, although their presence had not been suspected before operation. Among those cases grouped under the heading miscellaneous were four of duodenal ulcer, one of duodenitis, one of cholangeitis, one of myoma in the anterior wall of the stomach, one of Lane's kink, one of cholecystoduodenal fistula and one of accessory lobes of the liver.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS CHOLELITHIASIS ONLY

Chart 2 represents diagrammatically those cases in which operation was done after a diagnosis of gallstones had been made preoperatively. In all these cases, sufficient pathologic change was demonstrable in the gallbladder to warrant its removal, but gallstones were present in only 84.8 per cent. In 28.9 per cent of the cases associated chronic appendicitis was found, in 2.5 per cent subacute appendicitis, in 12.7 per cent hepatitis, in 7.8 per cent pancreatitis, and in 1.1 per cent cholangeitis. It is suggested, therefore, that the diagnosis of cholelithiasis is not so easily made as one is frequently led to believe. In this group cholecystitis only was found in 15.2 per cent, and yet the symptoms were obviously sufficiently severe to prompt the preoperative diagnosis of cholelithiasis.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS EITHER CHOLECYSTITIS OR CHOLELITHIASIS

Chart 3 includes cases in which a preoperative diagnosis either of cholecystitis or of cholelithiasis had been made, and represents a review of 879 cases. In order to facilitate consideration of these cases, they have been subdivided into groups as follows:

Group 1.—In this group, chronic cholecystitis, with or without stones, was discovered at operation and other abnormalities were not discovered. In 35.6 per cent of the cases, a chronically inflamed gall-

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bladder was found. In 6.6 per cent, there was evidence at operation of subacute inflammation but in none of these was there any notation on the chart that a subacute condition had been suspected before operation. Although, occasionally, a subacutely infected gallbladder is not productive of signs characteristic of this condition, the history usually includes some data which would aid in its preoperative recognition. There may be chills or fever or leukocytosis. Usually there

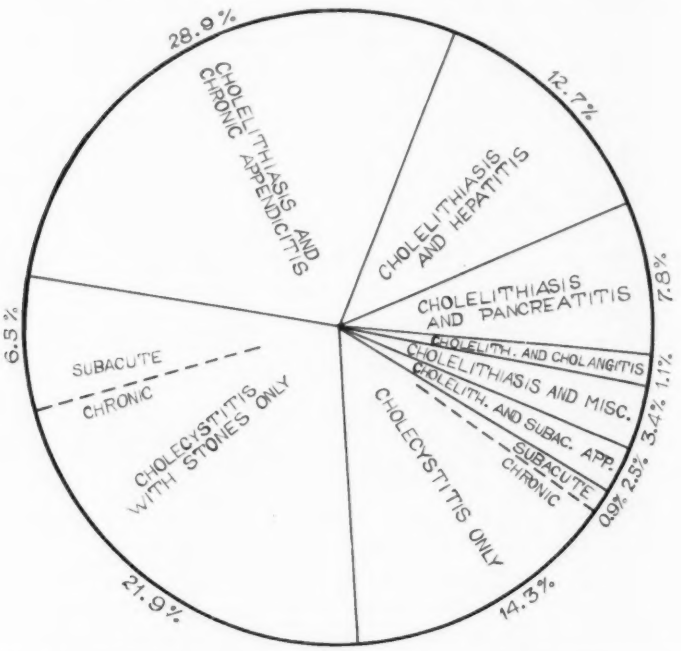

Chart 2.—Conditions found at operation in 592 cases in which the preoperative diagnosis was cholelithiasis only: *Misc.* indicates miscellaneous conditions as follows: duodenal ulcer, four cases; gastric ulcer, one case; ulcer near the fundus of the gallbladder, one case; carcinomatous growth of the common and cystic ducts, one case; carcinoma in the fundus of the gallbladder, one case; questionable carcinoma of the pancreas and common bile duct, one case; questionable carcinoma of the pancreas, one case; carcinoma of the liver, one case; cyst of the liver, one case; cyst of the wall of the gallbladder, one case; accessory liver, one case; angioma on the surface of the liver, one case; adenomyoma and epithelioma of the gallbladder, one case; adenoma at the fundus of the gallbladder, one case; adenoma of the abdominal wall with hyperplasia of the epidermis, one case; inflammatory lymph node filled with pigment, one case; fibroma of the gastrohepatic omentum, one case; diverticulum of the gallbladder, two cases; questionable duodenal diverticulum, one case; Lane's kink, one case, and cholecystoduodenal fistula, two cases.

is definite, localized tenderness and, not infrequently, rigidity of the overlying abdominal wall. In 58 per cent of the total number of cases included in this group, some disease besides that mentioned in the preoperative diagnosis was found at exploration.

Group 2.—Cholecystitis and hepatitis, cholecystitis and pancreatitis, or cholecystitis and cholangeitis were found at operation in cases classified in this group. Much has been written regarding the relationship

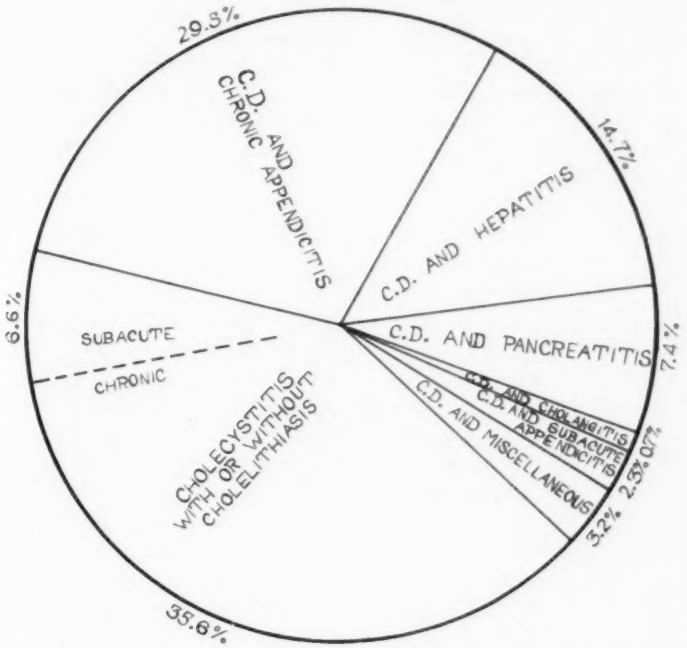

Chart 3.—Conditions found at operation in the total series of 879 cases in which the preoperative diagnosis was either cholecystitis or cholelithiasis: *C.D.* indicates cholecystic disease, which here includes cholecystitis, cholelithiasis, or both.

of disease of the gallbladder to hepatitis, pancreatitis and cholangeitis. In this series of cases, the surgeon's diagnosis of these complications was accepted. In 14.7 per cent of cases, hepatitis was found associated with the pathologic condition of the gallbladder. In 7.4 per cent of the cases, pancreatitis was a complication, and cholangeitis was found in 0.7 per cent. Inflammatory changes in the liver occur frequently when there is infection in the gallbladder.

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Mentzer [2] carried on an extensive study in this field. His material was obtained from 548 cases in which cholecystitis or cholelithiasis was found at necropsy. He studied sections from different regions of the liver and concluded that "the cases of noninflammatory disease of the gallbladder (minor gross lesions such as adenomas, diverticula, adhesions to adjacent organs without other evidence of disease of the gallbladder and cholesterosis) show a relatively small percentage of associated hepatic disease, 60 per cent, as compared with the definitely inflammatory diseases, such as gallstones, 97 per cent." Pancreatitis is a more rare complication of disease of the gallbladder. Mayo [3] stated that pancreatitis is found associated in 7 per cent of cases in which gallstones are present. In the series under consideration, there was evidence, on microscopic examination, of some degree of pancreatitis in 7.4 per cent of the cases of cholecystitis and cholelithiasis, taken together.

Cholangeitis seems to be a rare complication of disease of the gallbladder; it occurred in only 6 of the 879 cases included in this group.

Group 3.—Chronic, acute or subacute appendicitis was found at operation in this group. The lesion most commonly found associated with cholecystitis or cholelithiasis was chronic appendicitis; in 31.8 per cent of the cases, there was associated disease in the appendix. Undoubtedly this percentage would be still greater but for the fact that in a number of cases appendectomy had been performed before the patients came to the clinic. The frequency of this complication must not lead one to attach too much significance to it. Although a chronically inflamed appendix may, in a limited number of patients of a particularly sensitive make-up, be productive of some dyspepsia, it is debatable whether in the majority of the cases under present consideration, the history was greatly influenced by the presence of this complication. What seems of greater significance is the fact that in approximately 2 per cent of these patients acute or subacute appendicitis remained sufficiently masked in the syndrome of disease of the gallbladder to avoid detection by the examining physician. The relatively greater severity of symptoms of disease in the upper part of the abdomen may have led these patients to ignore the distress in the lower abdominal segment. Thus they might have failed to mention having pain in the region of the appendix.

It must also be remembered that occasionally an acutely inflamed appendix will cause such mild symptoms that they may be considered

2. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, Surg. Gynec. Obst. **42**:782, 1926.

3. Mayo, W. J.: Pancreatitis Resulting from Gallstone Disease, J. A. M. A. **50**:1161 (April 11) 1908.

of trivial significance. Nevertheless, one wonders whether more careful general examinations might have revealed definite tenderness in the lower part of the abdomen and thus might have led to correct diagnosis more frequently.

Group 4.—In this group has been placed a large variety of the less common complications found in association with cholecystitis or cholelithiasis. A further subdivision of this group has been made to facilitate discussion. Several reports of cases will be included.

Duodenitis: The patient had had dyspepsia at intervals for several years, with much gas and pain in the upper right quadrant of the abdomen. Distress was worse two hours after meals. Greasy and fried foods usually had been followed by dyspepsia. At operation, cholecystitis and definite duodenitis were found. It is difficult to state which lesion could be held accountable for the symptoms. Although the gallbladder showed enough evidence of involvement to warrant its removal, it would seem probable that the symptoms were related to the duodenitis. It has been pointed out by one of us (Rivers)[4] that duodenitis frequently is responsible for a syndrome such as that described in this case.

Gastric Ulcer: This patient had had intervals of colicky epigastric pain for twenty-nine years. The distress was described as a colicky pain referred through to the back, relieved by vomiting and usually lasting a few hours. The acidity of the gastric content was low. In all probability, the symptoms were due to the gallstones.

In 2 per cent of patients operated on for gastric ulcer, associated disease in the gallbladder was found. Reliable evidence of the presence of an active ulcer is the clinical history. Healed or quiescent ulcers are not uncommon.

Duodenal Ulcer: There were eight cases in which disease of the gallbladder was associated with duodenal ulcer. In none of these eight was there evidence roentgenologically of duodenal deformity, but in four cases the Graham-Cole method of roentgenography gave evidence that the gallbladder was diseased. It would appear that the clinician was unduly influenced in making his diagnosis by the roentgenologic results found in these cases. Abstracts of two illustrative cases follow:

In one case, the presence of both the ulcer and the gallstones should have been suspected. There was a history of colicky epigastric pain, coming in spells, and requiring hypodermic injections of hypnotics for relief. In addition, the history suggested peptic ulcer; that is, there had been epigastric distress from two to three hours after meals which had been relieved by the taking of food. The other patient

4. Rivers, A. B.: A Clinical Study of Duodenitis, Gastritis and Gastrojejunitis, Pennsylvania M. J., to be published.

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complained of colicky epigastric pains radiating through to the back. They had come on in spells, and at times hypodermic injection of morphine had been required for their control. The symptoms in this case were obviously related to the gallstones. At operation, duodenal ulcer and cholelithiasis were discovered.

Cholecystoduodenal Fistula: In this series, there were four cases in which a fistula was found to exist between the gallbladder and the duodenum. We believe that these cases are of sufficient importance to warrant a brief review of the histories.

The first patient had had a vague type of dyspepsia usually associated with migraine at intervals for seventeen years. Three years before the patient came to the clinic, severe pain had appeared in the upper right quadrant of the abdomen, radiating through to the back and to the right shoulder. Intermittent attacks had come on in spite of careful diet. There had been one severe spell recently, with pain so severe that the entire right side of the abdomen had seemed paralyzed. The gallbladder was not visualized by the Graham-Cole method. At operation, the gallbladder was found to be almost completely destroyed. Gallstones were not present. There was a fistula between the gallbladder and the duodenum.

The second patient, a woman, aged 59, had had an attack of acute indigestion accompanied by chills, fever, vomiting and very severe pain in the upper right abdominal quadrant about twelve years before coming to the clinic. At that time her temperature had been elevated for from three to four days; she had been in a stupor for several days; jaundice had been intense, and she had been obliged to remain in bed for thirteen days. Since this attack, there had been much gas and belching after ordinary meals, especially if they contained fatty foods. She had not had any more acute attacks. By the Graham-Cole method, the gallbladder gave only a faint shadow. At operation, a perforation between the gallbladder and the duodenum and one gallstone were found.

The third patient, a woman, aged 40, had had a severe attack of epigastric pain before she came to the clinic; this had radiated to the upper right quadrant of the abdomen and through to the back. Morphine had been necessary for relief. For the following two years, she had had frequent attacks similar to the one just described. Three weeks before she entered the clinic she had had a very severe attack of pain in the right upper abdominal quadrant and back, had perspired freely and had had chills and vomiting; her temperature had been very high. Three days after the onset of the pain she had become jaundiced. At brief intervals following this, she had had severe stabbing pains in the upper right part of the abdomen. At operation, the gallbladder was found to be contracted. There were multiple gallstones, and a fistula was found between the gallbladder and the duodenum.

The fourth patient, a woman, aged 51, had had some dyspepsia for ten years. Fried, greasy food had caused belching and nausea. At intervals she had had some pain in the upper right abdominal quadrant, which had radiated to the right shoulder. One year before she came to the clinic, she had had a severe attack of pain which had required three hypodermic injections of morphine for its control. Since then, she had had an attack of acute indigestion about once every three months. On a few occasions, she had vomited blood during these attacks. The roentgenogram of the gallbladder, made according to the Graham-Cole

method, showed only a faint shadow. Stones could be visualized. At operation, the gallbladder was found to be full of pus and stones. It had ruptured, leaving a fistula extending to the duodenum.

Naunyn [5] reviewed 384 cases of biliary fistula. Ninety-three of these were of the cholecystoduodenal type. The most common of the billiary fistulas are those between the gallbladder or biliary ducts and the intestine. Among these, the cholecystoduodenal fistula is the one most frequently seen. These fistulas may develop in several ways. The wall of the gallbladder may rupture, forming an abscess, and this in turn may rupture through into the duodenum. At other times, adhesions from repeated infections seal the gallbladder to the duodenum so that a perforation of the wall of either the gallbladder or a bile duct may lead directly to the formation of a fistula.

In one of the cases just reviewed gallstones were not found. It is possible, of course, that stones already had passed through the fistula into the intestine at the time the patient was operated on. The earlier history of jaundice further suggests such a succession of events. That fistulas may develop in acute conditions of the gallbladder, in the absence of gallstones, seems entirely possible, but actually this complication probably occurs infrequently, in the absence of stones in the gallbladder or bile ducts.

In the four cases just reviewed the clinical histories did not offer any definite diagnostic criteria which would lead one to suspect the presence of cholecystoduodenal fistula. The presence of complicated cholecystitis is suggested in all instances, however, by the unusually severe and protracted attacks of pain as well as by the severe chills and increased temperature, continued over a period of many days. The persistence of chills and fever, and the associated profound prostration, might suggest empyema of the gallbladder, but the severity of the pain seems to be out of all proportion to that usually experienced with this complication.

We are at present reviewing a large series of cases of cholecystoduodenal fistula and it is hoped that other data may be gathered which will give us further diagnostic criteria regarding this interesting complication.

Malignant Conditions: The cases in which malignant conditions were found during operations on the gallbladder seem of sufficient importance to demand individual consideration.

Carcinoma of common and cystic ducts. A man, aged 59, had begun to have attacks of severe pain in the upper part of the abdomen at the age of 51. The pain had been referred through to the back, and hypodermic injection of hypnotics had been necessary to control it. When the patient was about 55 years of

5. Naunyn, Bernhard: A Treatise on Cholelithiasis, London, The New Sydenham Society, 1896, p. 143.

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age a sore spot had developed in the right infracostal region. This had remained sore at all times. He had lost 10 pounds (4.5 Kg.) in five years. Roentgenographic examination by the Graham-Cole method revealed a faint shadow. At operation a small stone was found in the common bile duct. The gallbladder was large and acutely inflamed. A mass, about 2.5 by 2 cm., was growing on the outer side of the cystic duct, at its juncture with the common bile duct. The gallbladder was removed. Choledochotomy was performed, and the growth was removed. It was found to be an adenocarcinoma.

Carcinoma of the liver. A patient, during operation for carcinoma of the rectum, had been found to have gallstones. Intra-abdominal metastasis was not found. At an operation seven months later, undertaken because the patient was having frequent severe attacks of pain in the upper right quadrant of the abdomen, two carcinomas of the liver besides the gallstones were found. In this case, the primary carcinoma in the rectum probably was the source of these lesions.

Carcinoma of the gallbladder. A woman, aged 50, had for twenty years had intervals of upper abdominal pain which had not radiated. The attacks had endured for from twenty minutes to one hour and at times morphine had been necessary to control the pain. At first these spells had occurred infrequently; during the past year, they had come on once or twice every fortnight. At operation, a distended gallbladder containing stones was found. The gallbladder was removed. During the laboratory examination, an adenocarcinoma was found in the fundus.

Adenomyoma and epithelioma of the gallbladder. A woman, aged 58, had had spells of colicky pain in the upper right quadrant of the abdomen for eleven years, the attacks becoming increasingly frequent. One week prior to consultation at the clinic she had had a severe attack of pain which had been accompanied by chills and fever. There had not been jaundice. At operation, the gallbladder was found to be chronically inflamed and to contain stones. In the laboratory, an adenomyoma was found in the submucosa and a microscopic epithelioma in the mucosa.

Carcinoma of the gallbladder and bile ducts is not a rare complication of disease of the gallbladder. Mayo [6] found that carcinoma of the gallbladder was present in 2 per cent of a series of cases of cholelithiasis studied by him. For many years the relationship of gallstones and carcinoma of the gallbladder has been noted. Klebs and Willigk,[7] in 1869, suggested that gallstones were the cause of carcinoma of the gallbladder. Courvoisier [8] found gallstones in seventy-four of eighty-four cases of carcinoma of the gallbladder. We know of no reliable diagnostic criteria which can be employed in early cases of malignant disease of the gallbladder or bile ducts. In early cases, surgical operation offers a reasonable chance of cure. Later, when the diagnosis of this complication is suggested by loss of weight, cachexia and a mass in the region of the gallbladder, operation is usually of no avail.

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6. Mayo, W. J.: Carcinomata of the Gall-Bladder and Biliary Passages, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic **2**:144, 1910.

7. Klebs and Willigk, quoted by Naunyn (footnote 5).

8. Courvoisier, L. G.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890.

Carcinoma of the pancreas. There were two cases in which carcinoma of the pancreas was found. The first patient, a woman, aged 65, had had a brief period of dyspepsia at the age of 64. Then, at intervals, she had had a transitory pain in the upper part of the abdomen which had been accompanied by some gas and bloating. Six weeks before coming to the clinic she had begun to notice some jaundice. This had become progressively deeper. At intervals she had had severe pain in the upper right quadrant of the abdomen, for the control of which morphine had been required. There was a small mass in the upper right abdominal quadrant. This was fairly well fixed, and was not tender. It moved somewhat with respiration. At operation, a large, distended gallbladder was found. There were large masses in the head of the pancreas which had every clinical appearance of being malignant.

The second patient, a man, aged 62, two years before coming to the clinic had begun to have attacks of indigestion, characterized by pain in the epigastrium, much belching, and chills and fever. These attacks had recurred at intervals of about two months. Several months prior to examination, he had begun to have chills and fever, which had persisted for about a month. Then he had become jaundiced and this condition had continued until the time of operation. Exploration revealed chronic cholecystitis and stones in the gallbladder and bile ducts. The head of the pancreas was enlarged and hard. It was assumed that this hardness was due to a malignant condition.

Carcinoma of the pancreas, unless it occurs in the head of the organ, is likely to be overlooked. When it is situated in the head of the pancreas, its presence frequently can be suspected because of the attendant, progressive jaundice without colic, the palpable gallbladder and cachexia. Eusterman studied a series of 138 cases of carcinoma of the pancreas. He found that in only about half the cases were there symptoms which suggested the presence of the lesion.

Other Complications: The following complications are not of great importance but are included because they complete the record of pathologic entities found during operation on the gallbladder after a simple preoperative diagnosis of cholecystitis or of cholelithiasis had been made. Diverticulum of the gallbladder was found twice. Accessory liver and Lane's kink were also found twice. The remaining conditions were found once: diverticulum of the duodenum, ulcer near the fundus of the gallbladder, myoma of the anterior wall of the stomach, angioma on the surface of the liver, adenoma at the fundus of the gallbladder, cyst of the wall of the gallbladder, cyst of the liver and inflammatory lymph node filled with pigment.

SUMMARY AND CONCLUSIONS

The diseases found in association with cholecystitis or cholelithiasis, when one of these has been considered the pathologic process of major importance, are represented graphically in charts 1, 2 and 3.

Analysis of the 879 reports included in this group revealed the presence of subacute cholecystitis or of subacute appendicitis in seventy-

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eight instances. Additional care in obtaining histories, and especially careful general examination, should tend to lessen error in the recognition of these complications.

Gallstones were discovered at operation in 106 cases (12.1 per cent) when preoperatively a diagnosis of cholecystitis only had been made. Frequently, gallstones are not productive of severe pain.

Gallstones were not found at operation in about 15 per cent of the cases in which a preoperative diagnosis of cholelithiasis had been made. It would appear that the syndrome of cholecystitis frequently may include pain which is sufficiently severe to suggest the presence of gallstones.

The most significant of the complications discovered during operation performed for cholecystitis or cholelithiasis was found to be carcinoma involving the gallbladder, bile ducts or liver. Careful search through these histories did not reveal data which could have aided in the preoperative recognition of these complications.

Cholecystoduodenal fistula was found as one of the rare complications of disease of the gallbladder. This series included four such cases. Although it would have been impossible to diagnose this condition from the histories, the presence of some complications causing peritoneal irritation could have been suspected because of the unusually severe and protracted pain and because of the marked local and systemic reaction which was evident in each of these cases.

It would appear that modern diagnostic methods, correlating reliable laboratory data and carefully recorded histories, leave less than might be assumed for the surgeon to discover. The margin of safety in the liver permits much destruction of that organ before any symptoms are produced; mild hepatitis will go undiagnosed for a long time to come.

The surgeon's diagnosis of pancreatitis is always questionable as it is largely determined by the enlargement and induration present. The medical diagnosis of pancreatitis is still unreliable.

The presence or absence of gallstones, or the question whether the inflammatory reaction in the gallbladder is acute or subacute, is not of vital importance in a case of surgical cholecystitis.

Peptic ulceration of the stomach and duodenum, like gallstones, usually lends itself to easy diagnosis, and if active should be recognized from the history in spite of negative roentgenographic data.

Certainly better means of recognizing carcinoma are needed but odd, miscellaneous lesions probably will always be a surprise to the clinician after abdominal section.

THE TIME FACTOR IN THE ACTION OF PANCREATIC ENZYMES *

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In an article published about a year and a half ago, Dr. Anthony Bassler [1] made the following statements:

1. All proteolytic enzymes are dual in their action of conversion. This is true of the one in the stomach as well as of that in the pancreatic juice, both of which require outside activation, that of the stomach from hydrochloric acid and that of the pancreas from a product of the duodenal mucosa (enterokinase).

By this I judge he meant that some other agent is necessary to activate these enzymes. Certainly he cites hydrochloric acid as being necessary to activate pepsin. As this may cause misunderstanding, let me say that what pepsin needs for activation is a medium in which the hydrogen-ion concentration is within certain limits. The same factor is necessary for trypsin. Therefore, no more than diastase and lipase are they dual in their action of conversion.

He remarked that the action of the proteolytic enzymes is slow and went on to say:

2. As a general rule, this is not true of the diastatic ferments and in my work on diastatic activity with specimens from human beings and from animals, I found that in their action diastatic ferments closely correspond to a catalyzer; the action requires no time, incubation is almost unnecessary and it occurs at any reasonable temperature, even one that is considerably lower than that of the body. If one prepares tube 1 in the original test (namely, adding 1 cc. of duodenal return to 4 cc. of the starch solution) shakes it at once and tests for sugar with Benedict's or Fehling's solution, the sugar reaction will somewhat depend on the amount of diastatic ferment present; the test, however, is not accurate. Incubation for a considerable period of time does not cause much greater reaction. All that is necessary is to allow the mixture to stand for a minute or two at room temperature and definite conversion will occur.

Dr. Bassler was suggesting in this article the advantages of his starch method over a saccharogenic method [2] which I described in this journal about a year before. As his claim was mainly based on the reasoning quoted, it seemed that the following investigation might be of interest.

* Submitted for publication, Aug. 26, 1929.

* From the Gastro-Intestinal Clinic of the Johns Hopkins Hospital.

1. Bassler, A.: Arch. Int. Med. **41**:18 (Jan. 1) 1928.

2. Martin, L.: Arch. Int. Med. **39**:343 (March) 1927.

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METHOD OF INVESTIGATION

Pancreatic Extract.—Five grams of powdered pancreatic extract was dissolved in 50 cc. of distilled water by shaking. This mixture was allowed to stand for at least four hours and was then filtered through Whatman no. 12 filter paper and a Mandler filter. The clear filtrate was then diluted with phosphate buffer[3] of p_H 7.7 to 1:250 or 1:500 (adjusted so that the 30 minute tube would about equal the standard used).

One cubic centimeter of the diluted solution and 1 cc. of 1 per cent soluble starch solution (in phosphate buffer, p_H 7.7) were pipetted into Folin and Wu dextrose tubes, mixed and incubated for varying lengths of time. The tubes that were to be incubated longest were put in first so that all the tubes could come out at once, and the starch was not added to the Folin and Wu tube until just before it was to be incubated. The amount of sugar in each tube was then determined by the Benedict modification of the Folin and Wu method of determining blood dextrose.[4] In table 1 are shown the results of three experiments.

Duodenal Return.—Pancreatic enzymes were obtained by drainage through a small caliber (no. 14 Levine) tube placed in the duodenum and kept there during

TABLE 1.—*The Effect of Incubation on the Power of Diastatic Enzymes in Pancreatic Extract to Convert Starch Into Sugar*

Minutes Incubated	Amount of Dextrose in Milligrams		
	Experiment 1	Experiment 2	Experiment 3
5	Too pale to read	Too pale to read	Too pale to read
10	Too pale to read	Too pale to read	Too pale to read
15	...	42	60
20	37	72	61
30	54	105	100
35	69	...	...
40	...	182	143
60	71	400	286

the entire process. The position of the tube was verified by fluoroscopy. When the tube was in place, about 40 cc. of 33 per cent magnesium sulphate was injected to start the flow of bile and pancreatic juice. The return was collected in 15 cc. centrifuge tubes until the drainage stopped. If more was desired, a second injection of magnesium sulphate was made. The tube containing the clearest and darkest fluid (B bile) was used for the determination of diastase. This tube was centrifugated at high speed for fifteen minutes. A small amount of the supernatant fluid was diluted to 1:600 with the phosphate buffer.[3] The method of diluting a 1:600 solution was given in my original article.[2]

One cc. of the 1:600 dilution was pipetted into each Folin and Wu tube and treated with 1:0 cc. of 1 per cent starch solution in exactly the same manner as the pancreatic extract. The results may be seen in table 2.

The last case is that of hepatosis from arsphenamine intoxication. There was tremendous jaundice; no bile was excreted into the intestine. Consequently, the duodenal return was almost colorless and the results of the test were not influenced in any way by bile. There is no difference between the result in this case and that in the others.

3. Clark, W. M.: Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1925.

4. Benedict: J. Biol. Chem. **68**:759, 1926.

CONCLUSIONS

The tables demonstrate that there is a direct proportion between the length of incubation and the amount of dextrose produced. In a few of the experiments, the rise was not entirely uniform, but it will be noticed that in every experiment the thirty minute tube is greater than the five minute tube and less than the sixty minute. The cause of this uneven rise seemed to be in the mixing of the solution when diluting it 1:600; in the last three experiments the solution was thoroughly mixed and the rise was uniform.

A weak dilution of enzyme is necessary for this demonstration, as an undiluted mixture will be strong enough to quickly hydrolyze the starch completely. Such a complete hydrolysis will form enough dextrose and maltose to more than reduce the amount of alkaline copper sulphate used. This was explained in the original article.

TABLE 2.—*The Effect of Incubation on the Power of Diastatic Enzymes in Duodenal Return to Convert Starch Into Sugar*

	Amount of Dextrose in milligrams								
Incubated Minutes	Experiments								
	4	5	6	7	8	9	10	11	12
5	71	83	55	71	114	69	114	125	95
10	67	79	60	89	77	91	174	133	125
15	77	97	54	80	...	111	210	143	154
20	...	105	60	89	236	100	265	200	182
25	...	...	...	...	262	...	...	...	...
30	117	111	60	98	282	125	365	225	223
35	...	...	...	...	...	133	400	...	...
40	180	149	71	108	...	...	...	...	286
60	143	143	91	167	396	...	...	500	334

COMMENT

There are a few other comments in Dr. Bassler's article that are worthy of consideration. In his conclusions, he makes the following general statement:

> 3. Dissociation of pancreatic enzymes does not occur in disorders and diseases of the gland. If amylopsin is deficient, there will also be a lack of trypsin.

In a former article I went into the work of various investigators at some length, and presented phases of their work that made me think that such a dissociation did not occur, in spite of some evidence that a few of these men advanced. However, there is no proof that dissociation of enzymes is an impossible state of affairs. Perhaps Dr. Bassler has the facts at hand to warrant this "ex cathedra" statement; I cannot find them in his article.

SUMMARY

If the pancreatic enzyme, diastase, is diluted sufficiently so that it does not hydrolyze starch too rapidly, it is possible to demonstrate a definite relationship between the length of incubation and the amount of starch hydrolyzed to dextrose or maltose.

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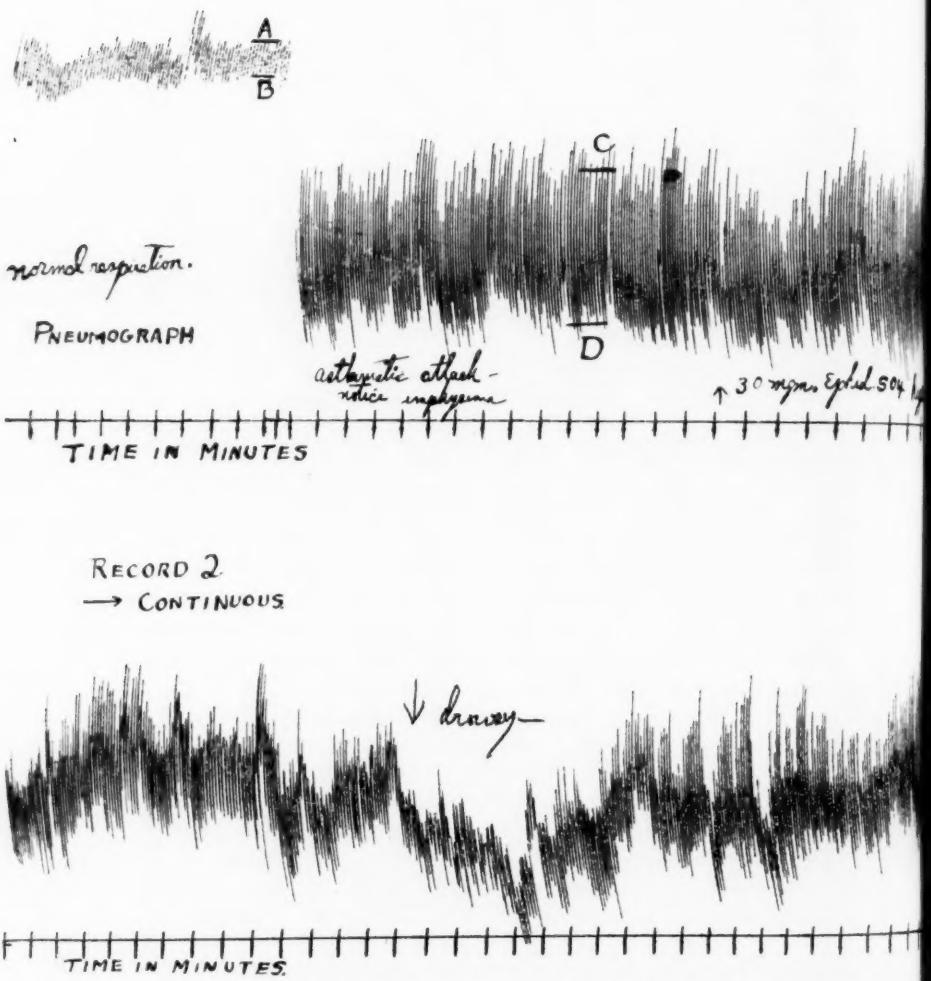
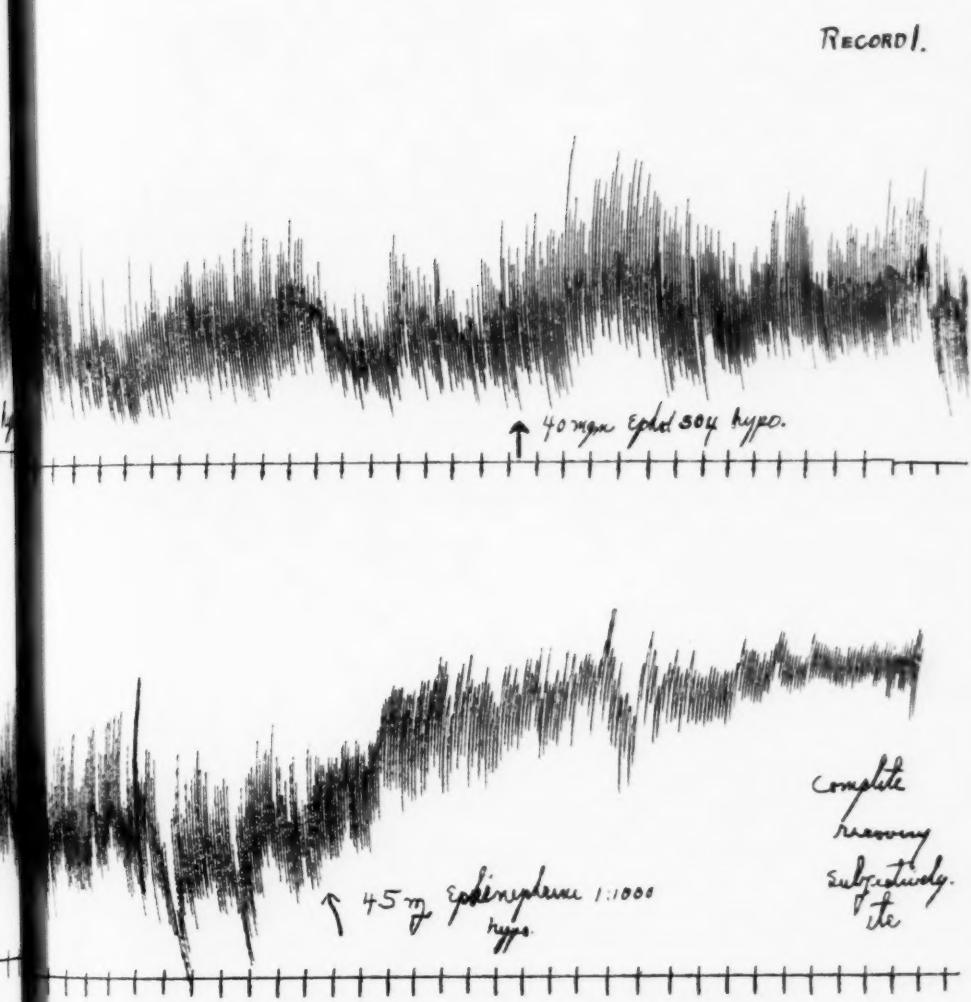


Fig. 1.—The influence of ephedrine on an acute attack of asthma. Reproduction of a type experi... upstroke of the lever recorded the expiratory movement. The letters *A* and *B* represent the limit... development of asthma.



wing the respiratory movements and volumes obtained by means of a pneumograph and tambour. The expiratory and inspiratory phases under normal conditions; *C* and *D*, similar points after the

of emphysema. The alveolar carbon dioxide readings obtained during the attacks were apparently normal, but it is doubtful whether the values noted during the attack were correct, as the type of breathing pointed to an increased carbon dioxide tension and it is quite probable that under the conditions, a true alveolar sample was not obtained. The circulatory changes were compensatory and of secondary importance. On administration of epinephrine, subjective relief was apparent within one minute, and symptomatic recovery was generally complete within from six to ten minutes, as is shown by the respiratory data in the accompanying table.

The Influence of Epinephrine on the Symptoms of an Induced Asthmatic Attack*

		Administration of Epinephrine			
Observations	Normal	During Attack	2 Minutes Later	10 Minutes Later	Comment
Temperature	37.2 C. (98.9 F.)	37.2 C. (98.9 F.)	37.4 C. (99.3 F.)	37.2 C. (98.9 F.)	
Respiration rate	18	28	21	19	
Tidal volume	500 cc.	350 cc.	725 cc.	545 cc.	
Minute volume	9,000 cc.	9,800 cc.	15,225 cc.	10,355 cc.	
Vital capacity	4,100 cc.	1,500 cc.	4,400 cc.	4,300 cc.	
Alveolar CO_2	3.9%	3.9%†	3.9%	3.9%	
Blood pressure	104/70	130/84	122/72-118/60	112/65	Dyspnea, emphysema
Heart rate	77	100	90	84	Counted
Time of entire systole	0.27 seconds	0.24 seconds	0.23 seconds	0.25 seconds	Optical records
Time of entire diastole	0.608	0.36-0.40	0.33-0.31	0.43 seconds	Optical records
Total cycle	0.875	0.6 -0.64	0.56-0.54	0.78	Optical records
Delay at rise	0.12-0.11	0.1 -0.095	0.12-0.11	.....	Optical records
Delay at incisura	0.12-0.11	0.1 -0.10	0.125-0.11	.....	Optical records
Velocity of pressure wave	5.04 m./sec.	5.8 m./sec.	6.8 m./sec.	5.04 m./sec.	Optical records

* The dose was 5 minims (0.3 Gm.) of a 1:1000 solution.
† Figure given is not reliable.

A comparison of the efficiency of epinephrine, ephedrine and atropine in relieving the changes in respiratory rates, volumes and grossly the degree of emphysema produced by an asthmatic attack developed by air hunger is shown in figure 2. Each curve represents the median observation from several experiments of the same type. The figure was constructed by plotting the median measurements of the actual changes observed in the several experiments on the time of action. (The actual records as illustrated by figure 1 inverted, as the lever moved downward during inspiration; i. e., figure 2 *B* would correspond roughly to figure 1 if the latter were turned upside down and read from right to left.)

The contrast between the efficiency of epinephrine and ephedrine as to the time of action in giving symptomatic relief from an induced asthmatic attack was striking. The administration of epinephrine gave symptomatic relief, which was apparent within from thirty to sixty seconds and was reflected by the rapid disappearance of the choking sensation and emphysema, as illustrated by the prompt return of the

respiratory phases toward normal (fig. 2 *A*, *B* and *C*). The profuse sweating due to the dyspneic breathing subsided after two or three minutes, and after a short compensatory increased ventilation due probably to an increased alveolar carbon dioxide tension (developed during the attack), recovery was complete.

The subcutaneous administration of ephedrine sulphate in from 45 to 75 mg. doses was followed, in the majority of the tests, by a slow but

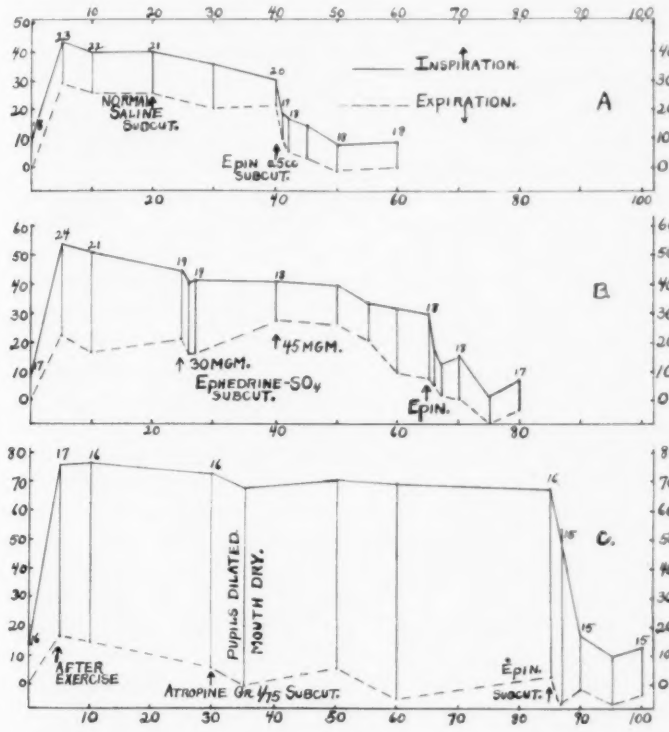


Fig. 2.—Graphic comparison of the efficiency of epinephrine, ephedrine and atropine on the course of a series of asthma reactions induced by exercise. Each curve represents the median of a series of experiments and was constructed by inverting the measured changes which developed as illustrated in figure 1, to show the alterations in the volume of the chest before and during an attack and after the administration of the respective drug. The numerals on the horizontal scale represent the respiratory rates per minute; those on the vertical scale, the change in the lever, by millimeters. *A* gives the median for five experiments; *B*, the median for four experiments and *C* the average of two experiments.

gradual alleviation of the symptoms. The ephedrine effect became evident after twenty-five minutes and extended over a forty to eighty minute period, as illustrated in figure 2 *B*. This likewise shows the rapid terminal recovery produced by epinephrine after a prolonged and incomplete ephedrine reaction.

The subcutaneous administration of $\frac{1}{75}$ grain (0.0008 Gm.) of atropine sulphate did not give relief from the symptoms during the fifty-five minutes succeeding the development of an attack, as shown in figure 2 *C*, although the pupils were widely dilated and the mouth became very dry within from four to seven minutes after the administration of the drug. This curve therefore, in the absence of any antiasthmatic action of atropine under the conditions of the experiment, may be utilized to illustrate the persistence over ninety minutes of asthmatic attacks which developed as a result of air hunger. Longer graphic records have not been obtained although subjectively attacks have persisted for eight hours, at which time epinephrine was necessary for relief.

The surgical correction of the deflected nasal septum did not significantly influence either the number or the severity of the allergic or reflex asthmatic attacks during the year following the operation.

The use of epinephrine, ephedrine or atropine for relief from the symptoms of asthma during the entire three year period indicates that the efficiency of these drugs, as judged from the degree of relief afforded, was quite similar to that noted with the induced attacks, as illustrated in figure 2. Epinephrine was the most effective, i. e., gave prompt relief in both mild and acute attacks. Atropine was the least effective of the drugs tested and was discontinued on account of undesirable action on the eye and salivary secretions. Ephedrine administered subcutaneously as a 3 per cent solution or taken orally in capsule form in from 45 to 90 mg. doses was effective in limiting the number of attacks or in alleviating mild attacks. Relief, however, required the prompt administration of one or two capsules daily on the first appearance of symptoms and for several days thereafter. In acute attacks, ephedrine was practically ineffective, as shown in figure 1, although all symtoms under such conditions, even after the ineffective administration of ephedrine, were promptly relieved by epinephrine.

The degree of effectiveness of ephedrine as noted in this series of studies is in agreement with those of numerous recent publications. Leopold and Miller,[1] in reviewing a mixed series of fifty-nine cases of asthma, observed that the drug gave complete relief in 56 per cent.

1. Leopold, S. S., and Miller, T. G.: Use of Ephedrine in Bronchial Asthma and Hay-Fever, J. A. M. A. **88**:1782 (June 4) 1927.

partial relief in 29 per cent and no relief in 15 per cent of all cases tested. Complete relief was obtained in all cases of the anatomic or reflex nasal type; 84 per cent of the cases of the allergic type reacted completely, while only 38 per cent of the infectious type showed complete relief. Corresponding observations were obtained by Munns and Aldrich,[2] on a series of 22 unselected cases. Stewart,[3] maintained that the therapeutic use of ephedrine in the treatment for asthma should be further limited, in that its chief use seems to be as a preventive; that is, it reduces the frequency and severity of the attacks in mild or chronic asthmatic conditions, while in acute attacks of either the simple or complex type, it is ineffective.

CONCLUSIONS

1. The asthmatic respiratory and circulatory changes are described which occur in a subject who is able to induce a typical attack of asthma by means of exercise.

2. During these induced attacks, the movements and volume of the chest were recorded by means of a pneumograph tambour arrangement. This method was utilized for comparing the efficiency of several antiasthmatic drugs.

3. Studies of the antiasthmatic efficiency of epinephrine, ephedrine and atropine on the course of comparable induced attacks of asthma as well as the routine use of these drugs in producing relief from allergic or reflex attacks over a three year period showed that the efficiency of these drugs from greatest to least was in the order named; i. e., epinephrine was effective in all attacks; ephedrine was most effective in relieving mild attacks or as a preventive, while atropine was unsatisfactory for either acute or mild attacks.

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2. Munns, G. F., and Aldrich, C. A.: Ephedrine in Treatment of Bronchial Asthma in Children, J. A. M. A. **88**:1233 (April 16) 1927.

3. Stewart, H. H.: Brit. M. J. **1**:293, 1929.

INSULIN INACTIVATION BY HUMAN BLOOD CELLS AND PLASMA IN VITRO

EFFECT OF NORMAL AND OF DIABETIC BLOOD ON INSULIN ACTION *

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Patients suffering from diabetes mellitus are known to have periods during which they do not respond properly to insulin. It is likewise well established that diabetes becomes worse during infection, injury or operation. These observations have aroused much interest and investigation in the past few years. It is interesting that seventy-five years ago Claude Bernard [1] was well aware of the danger of infection to diabetic patients.

Patients who temporarily or permanently resist insulin action are called insulin resistant or insulin refractory. The periods of resistance to insulin may be recurrent, ending in spontaneous recovery, or may be lasting, terminating in coma and death.

In July, 1925, E. K., a girl, aged 6 years, with severe diabetes, began to have peculiar reactions to insulin. On a constant diet and without any evident complication, she seemed to resist insulin action at one time and at another to have hypoglycemia on the same or smaller dosage of insulin. This was temporary and no infection was found. Dr. B. Schick suggested that this child might have a substance in her blood that inhibited insulin action.

By tests on rabbits we found that the patient's blood did affect insulin action. At the same time we were surprised at finding that normal blood, used as a control, also inhibited insulin action. The relative effect of normal and diabetic blood on insulin action is represented by the blood sugar determinations made before injection and hourly for three hours after the subcutaneous injection of the blood-insulin mixture into rabbits. It is evident that the diabetic blood was much more effective in preventing the action of the insulin than was the normal blood (table 1).

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* Submitted for publication, Sept. 12, 1929.

* From the Departments of Pediatrics and Laboratories of Mount Sinai Hospital.

* A preliminary report of this study was published in Proc. Soc. Exper. Biol. & Med. **26**:11, 1928.

1. Bernard, Claude, quoted by Mauriac, P., and Aubertin, E.: Presse méd. **34**:1633 (Dec.) 1926.

The figures in table 1 show clearly that 1.5 cc. of blood plasma from a diabetic or normal human being was inadequate to affect the blood sugar, but that 5 cc. of either plasma was sufficient to have a definite effect.

After the aforementioned observations had been made, numerous problems presented themselves, of which the following were studied:

1. Does the blood plasma of all human beings inactivate insulin in vitro and is it a quantitative reaction? 2. Do blood cells have the ability to inactivate insulin? 3. Is this reaction always greater with the blood of diabetic patients? 4. Are dilution of the mixture, viscosity, slow absorption or p_H change factors in inhibition by blood? 5. Do white blood cells or pus have greater power of inactivation than blood plasma or ordinary blood cells? 6. Is this inactivation greater during spontaneous infection or during artificially produced diseases simulating infection, such as serum sickness or phase after vaccine injection? 7. What are some of the properties of this inhibitory substance in the blood? Is it affected by heat, cold or p_H change; is the time of incubation a factor?

TABLE 1.—*Blood Plasma*

	Blood Plasma	0 Hours	1 Hour	2 Hours	3 Hours
E. K., diabetic	1.5 cc.	0.090	0.045	0.040	Convulsions
	5 cc.	0.115	0.095	0.068	0.090
Normal	1.5 cc.	0.102	0.055	0.060	0.056
	5 cc.	0.095	0.071	0.056	0.082

PROCEDURE

Unless otherwise stated, all studies were made as follows: The substance investigated (usually blood plasma or cells) was mixed with 3 units of Lilly's or Squibb's insulin which was diluted with physiologic solution of sodium chloride so that 1 cc. contained 1 unit of insulin. The mixture was usually made up to 10 cc., with physiologic solution of sodium chloride incubated at 37 C. for one hour; it was then injected subcutaneously into rabbits weighing 2 Kg., which were starved for the preceding twenty-four hours. For sugar determinations, blood was obtained from the marginal vein of the ear before injection and hourly for three hours afterward. Blood cells were obtained by centrifugation of citrated blood for fifteen minutes at high speed. They were not washed except in a few experiments used for comparison. Blood sugar determinations were made by the micromethod of Folin-Wu as modified by T. Kuttner.[2] Sugar determinations were done singly and were repeated on the filtrates when necessary.

EXPERIMENTAL DATA

The results of our experiments are presented in composite curves. Each point represents the average of several similar experiments which are presented singly in the succeeding tables. Throughout the ordinate

2. Kuttner, T.: Personal communication to the authors. The method is to be published.

TABLE 2.—*Control Experiment on the Blood Sugar of Rabbits, Showing the Effect of Subcutaneous Injection of Three Units of Insulin Previously Incubated with Saline Solution for One Hour at 37 C.*

Blood Sugar in Milligrams Before Injection	Blood Sugar in Milligrams After Injection			
	1 Hour	2 Hours	3 Hours	
98	62	58	..	Convulsion 2 hours
80	50	..	..	Convulsion 1¾ hours
84	58	47	..	Convulsion 2¾ hours
110	66	66	66	
102	65	..	..	Convulsion ½ hour
112	66	44	..	Convulsion 1¾ hours
113	72	40	..	Unsteady
111	54	43	..	Convulsion 2¼ hours
100	74	52	43	Convulsion 3 hours
92	62	44	38	
118	81	70	70	
85	62	58	68	Unsteady
75	45	45	40	Unsteady
66	66	55	44	Unsteady
92	66	70	50	Convulsion 2½ hours
83	44	44	44	
110	55	58	..	Convulsion 2 hours
112	58	58	..	Convulsion 2 hours
105	51	42	40	
108	56	50	..	Convulsion 2 hours
110	72	55	46	Unsteady
114	50	50	..	Convulsion 2 hours
110	55	50	50	Convulsion 2½ hours
Average 92	62	51	45	

TABLE 3.—*Studies on Rabbits with Normal Blood Plasma and Control, Showing the Effect of the Subcutaneous Injection of Various Amounts of Human Blood Plasma Previously Incubated at 37 C. for One Hour with Three Units of Insulin*

Amount of Plasma	Milligrams of Blood Sugar				
	Before Injection	After Injection			
		1 Hour	2 Hours	3 Hours	
15 cc.	112	110	110	106	
	100	100	100	102	
10 cc.	103	88	70	86	
	120	96	65	82	
	63	66	66	66	
	77	73	72	73	
	99	92	81	83	
	90	61	66	70	
	78	75	75	75	
	95	85	85	88	
	92	80	85	87	
	98	85	72	78	
	94	86	78	75	
	98	82	85	80	
	100	85	72	70	
	94	86	82	90	
Average	96	81	75	79	
5 cc.	95	71	56	82	
	83	66	64	53	Irritable
	97	70	61	55	
	94	75	71	57	
	94	68	55	75	
	98	76	65	75	
Average	93	73	66	69	
4 cc.	90	72	88	90	
	101	92	62	65	
	88	74	70	72	
3 cc.	95	60	49		
	115	75	46	40	
2 cc.	90	72	60	66	
	94	55	50	52	
	91	52	42	48	Convulsions 150 min.
1 cc.	102	55	50	49	
	105	56	52	58	
	90	65	40	49	

represents the sugar content of the rabbit in milligrams per hundred cubic centimeters of blood and the abscissa the time of determination, which always was before injection or at zero, and one, two and three hours after injection.

Chart 1 shows that the control group acted as was expected. Most of the animals developed marked hypoglycemia in one hour, which became more marked in the second and third hours. Eighteen of the twenty-five rabbits had convulsions. The convulsions nearly always

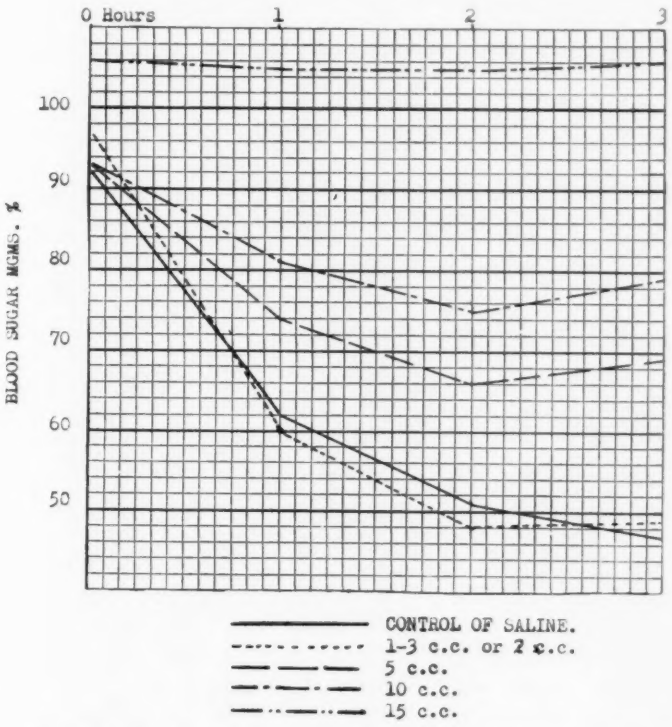

Chart 1.—The effect of various amounts of blood plasma on insulin action.

ceased and hypoglycemia was relieved within five minutes by the subcutaneous injection of dextrose solution.

When 1, 2 or 3 cc. of blood plasma was mixed with 3 units of insulin and injected, the blood sugar dropped almost as low as in the control rabbits, but convulsions were rarely observed. When 4 or 5 cc. of blood plasma was used, the usual insulin action was inhibited. When 10 cc. of blood plasma was used, almost complete

neutralization of the insulin action occurred, and with 15 cc. hardly any change in blood sugar could be noticed.

It is evident that not all rabbits responded in exactly the same way to any one procedure. That is probably due to a variation in individual reaction. By comparison with a number of similar experiments, however, a correct impression can be obtained.

TABLE 4.—*Experiment on Blood Sugar of Rabbit, Showing the Effect of the Subcutaneous Injection of Various Amounts of Human Blood Cells Previously Incubated at 37 C. for One Hour with Three Units of Insulin*

	Blood Sugar in Milligrams				
		After Injection			
Amount of Cells	Before Injection	1 Hour	2 Hours	3 Hours	
5 cc.	97	98	92	92	
	104	85	65	45	
	100	84	82	76	
	104	86	68	72	
	115	110	108	100	
	114	84	86	84	
	96	75	65	65	
	82	40	55	80	
	87	52	70	82	
	103	82	92	90	
	92	80	88	90	
	90	77	80	80	
	90	64	67	70	
	103	92	98	98	
	96	94	94	95	
	114	110	98	100	
	90	100	92	90	
	95	80	75	70	
Average	98	78	81	82	
3 cc.	90	75	70	70	
	90	58	55	60	
	92	65	70	75	
	90	85	80	80	
2 cc.	88	64	52	56	
	96	80	70	66	
	94	55	35	..	Convulsions 2 hours
	94	74	40	..	Convulsions 2 hours
	98	55	40	..	Convulsions 2 hours
	106	90	80	76	
	116	60	55	64	
	108	55	55	55	
	105	65	55	65	
	95	60	68	..	Convulsions 2 hours
	92	58	64	60	
	88	58	60	50	
	86	50	50	..	Convulsions 2 hours
Average	98	65	62	60	

Effect of Blood Cells on Insulin Action.—It was our impression that the inactivation of insulin was probably due to an enzyme-like substance. If this was true, blood cells, especially leukocytes and pus cells, should have a greater inhibitory effect on insulin action by virtue of their greater enzyme content.

The composite curve (chart 2) and tables 4 and 5 show that 5 cc. of blood cells gave the same reaction as 10 cc. of plasma and 3 cc. of blood cells that of 5 cc. of plasma. Although 2 cc. of cells was inadequate to cause much insulin inactivation, it was enough to make a definite inhibitory impression. Yet no consistent reaction was obtained with blood cells. It was therefore decided to lake the cells. Washed blood cells used as controls acted as did the unwashed cells.

TABLE 5.—*Experiments on the Blood Sugar of Rabbits, Showing the Effect of Laked Human Blood Cells Previously Incubated for One Hour with Three Units of Insulin at 37 C.*

	Blood Sugar in Milligrams				
		After Injection			
Amount of Cells	Before Injection	1 Hour	2 Hours	3 Hours	
	Laked Blood Cells				
5 cc.	108	92	98	98	
	96	84	94	95	
	114	110	88	100	
	90	100	92	90	
	92	92	90	95	
3 cc.	95	94	92	95	
	96	95	95	102	
2 cc.	102	94	90	90	
	98	96	98	90	
	97	95	87	96	
	93	80	75	90	½ hour incubation
	85	89	70	80	¼ hour incubation
	94	92	94	94	½ hour incubation
	92	85	92	88	¼ hour incubation
	92	92	92	90	½ hour incubation
	99	98	92	95	¼ hour incubation
Average	95	92	90	92	
1 cc.	92	82	78	75	
	88	75	70	76	
	93	76	72	75	
	102	90	75	70	
0.5 cc.	92	55	64	65	
	92	60	60	68	
	96	55	62	70	
	92	55	60	68	
	95	50	72	78	
	97	60	65	70	
	Washed Laked Blood Cells				
2 cc.	102	98	102	100	
	94	90	88	90	
1 cc.	95	85	90	92	
	98	82	80	95	

The blood cells were then laked with distilled water and a marked difference was observed. Two cubic centimeters of laked cells regularly caused complete neutralization, even more than did 10 cc. of plasma or 5 cc. of unlaked cells. One cubic centimeter of laked cells was more inhibitory than was 5 cc. of plasma or 3 cc. of cells intact. As little as 0.5 cc. of laked cells caused definite inhibition. It is therefore fairly evident that this inhibitory substance is mainly intracellular.

Effect of Diabetic Blood on Insulin Action.—After it had been demonstrated that the blood of patient E. K. had greater inhibition of the

insulin action, we compared other diabetic bloods with those of normal persons. The experiments in table 6 show the striking difference in the power of inhibition of insulin action existing between diabetic and nondiabetic blood.

Before speculating on an explanation of this observation, various controls were necessary to rule out the significance of dilution, viscosity of the blood or p_H of the blood (chart 3).

The question of dilution is answered by the many saline controls, in which 3 units of insulin was diluted to 10 cc. with physiologic solution

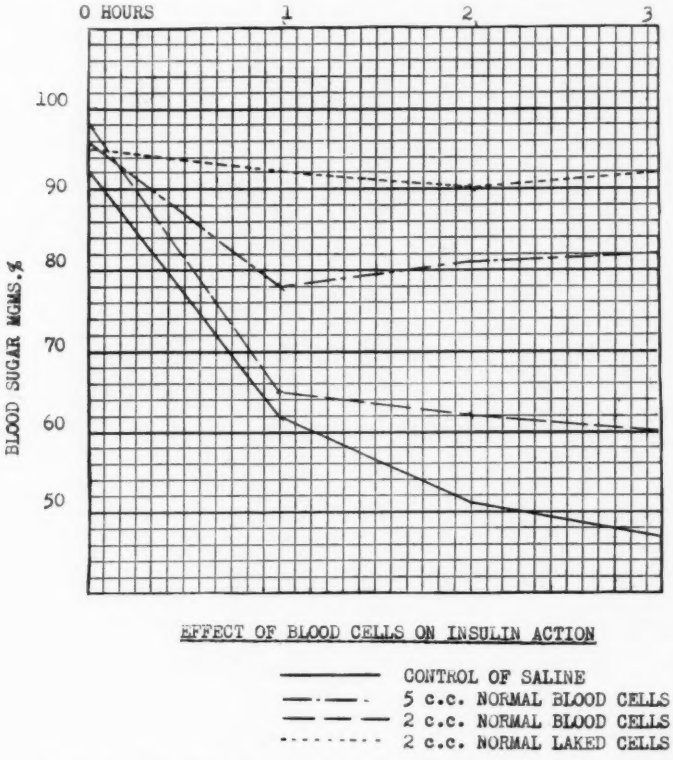

Chart 2.—The effect of blood cells on insulin action. The continuous line represents the control of saline; the long dash dot line, 5 cc. of normal blood cells; the long dash line, 2 cc. of normal blood cells, and the short dash line, 2 cc. of normal laked cells.

of sodium chloride. The results were similar to those seen from insulin alone. Agar-agar and egg albumin were used to study the questions of viscosity and adsorption. Here again the results were similar to those due to insulin alone.

TABLE 6.—*Rabbit Blood Sugar Curve, Showing the Effect of the Subcutaneous Injection of Various Amounts of Blood Cells of a Diabetic Patient Previously Incubated at 37 C. for One Hour with Three Units of Insulin*

	Blood Sugar in Milligrams			
		After Injection		
Amount of Cells	Before Injection	1 Hour	2 Hours	3 Hours
5 cc. of plasma or serum	115	95	98	90
	122	85	80	83
	85	85	85	85
	85	75	80	70
	95	85	85	80
	90	80	80	80
	108	110	94	90
	105	105	110	102
	105	100	100	95
	112	80	80	78
	105	66	104	100
5 cc. of cells	95	88	84	80
	110	105	100	96
	102	85	95	95
	105	80	88	80
3 cc. of cells	90	75	75	65
	95	73	75	70
2 cc. of cells	88	64	52	56
	98	78	75	68
	102	78	68	65
	112	76	64	68
	98	75	58	60
	106	77	62	70
	112	70	60	56
	110	62	50	50
	105	64	60	55
	Laked Diabetic Blood Cells			
2 cc. of cells	94	98	95	97
	96	95	95	95
1 cc. of cells	101	105	100	102
	92	90	92	96
	92	86	92	94
	99	74	91	96
0.5 cc. of cells	96	65	75	88
	91	76	84	86

TABLE 7.—*Control Experiments*

	Agar-agar				
		After Injection			
Amount of Cells	Before Injection	1 Hour	2 Hours	3 Hours	
	Agar-agar				
4 cc.	115	56	55	..	Convulsions 2 hours
6 cc.	112	55	55	..	Convulsions 2 hours
10 cc.	120	52	58	..	Convulsions 2 hours
	115	54	54	..	Convulsions 2 hours
	Egg Albumin				
6 cc.	102	62	42	40	Convulsions
8 cc.	108	58	46	40	Convulsions 2 hours
10 cc.	112	60	48	40	Convulsions
	107	60	45	40	Convulsions 2 hours
	Purified Horse Serum				
5 cc.	98	52	38	58	Convulsions
	94	48	50	50	Irritable
	96	50	48	48	Convulsions
	94	50	60	42	Convulsions

The question of p_H was more difficult to solve. It is known that insulin deteriorates in the presence of sodium and potassium hydroxide,[3] and becomes inactivated by an alkaline buffer mixture.[4] Its activity cannot be restored after destruction with sodium or potassium hydroxide, but can be restored by acidification with hydrochloric acid, after it has been inactivated by weak alkalis, as ammonium carbonate or ammonium hydroxide. Insulin becomes inactivated by alkali at p_H 7.2 or more

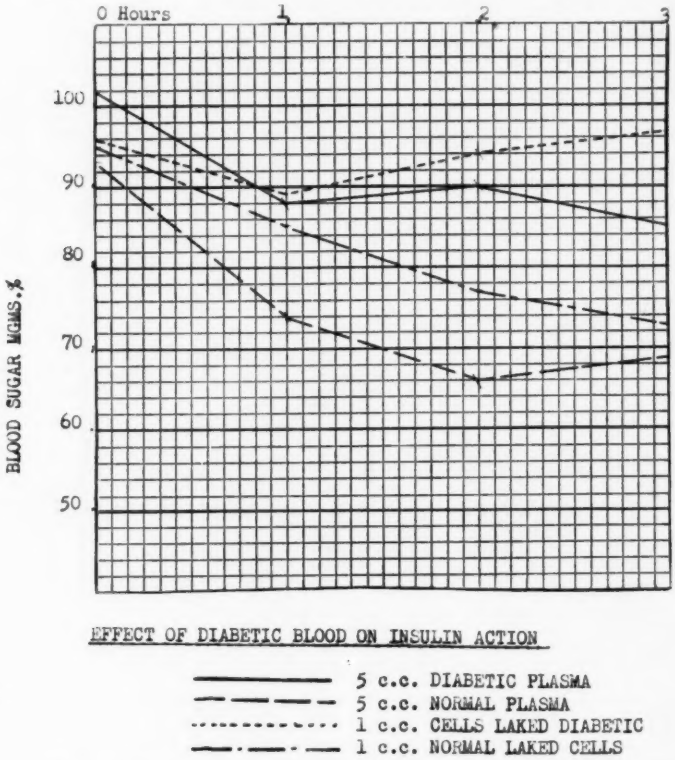

Chart 3.—The effect of diabetic blood on insulin action. The continuous line represents 5 cc. of diabetic plasma; the long dash line, 5 cc. of normal plasma; the short dash line, 1 cc. of laked diabetic cells, and the long dash dot line, 1 cc. of normal laked cells.

after many hours of incubation. Blood, after standing and being citrated, changes to a p_H of from 7.8 to 8.4. Our experiments were first to citrate blood which had been standing back to p_H 7.4 by the

3. Witzeman, E. J., and Livshis, L.: J. Biol. Chem. **58**:463 (Sept.) 1923.
4. Shonle, H. H., and Waldo, J. H.: J. Biol. Chem. **66**:467 (Dec.) 1925.

addition of tenth-normal hydrochloric acid. After that had been done, the usual insulin inhibition occurred.

If more insulin inhibition is to be expected because of the alkalinity at p_H 8, 5 cc. of blood plasma at that p_H might be expected to cause almost complete inhibition of 3 units of insulin. When 5 cc. of blood plasma at p_H 8 was tried, the effect on insulin was not unlike that obtained with 5 cc. of plasma at p_H 7.4. It was less than the inactivation

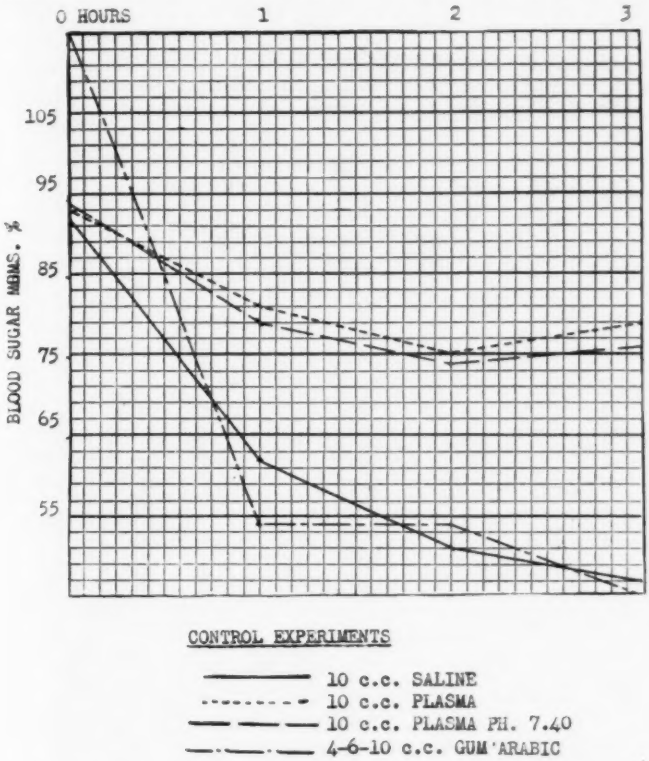

Chart 4.—Control experiments. The continuous line represents 10 cc. of saline; the short dash line, 10 cc. of plasma; the long dash line, 10 cc. of plasma with a p_H of 7.4, and the long dash dot line, 4, 6 and 10 cc. of gum arabic.

due to 10 cc. of plasma at p_H 7.4. Saline mixtures at from p_H 7.4 to 8 did not cause insulin inhibition, but at 9.2 mild insulin inactivation occurred. At p_H 6 blood plasma no longer inactivated the insulin. The p_H determinations were partly performed potentiometrically and partly by the La Motte colorimetric method. From these experiments, it seems

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fairly clear that at the p_H of normal blood insulin is inactivated in vitro by human blood plasma, but that this inactivation is not due to the change toward alkalinity on standing; at p_H 6 this inhibitory substance is ineffective. The foregoing is true for the period of incubation used in our experiments—from one to two hours.

From chart 5 and table 8 it is evident that diabetic blood is much more inhibitory than normal blood. The reason for this is entirely speculative since the few suggestions which might be made here have not as yet been adequately proved. First we have to consider the conception of Epstein and Rosenthal,[5] which is to the effect that in diabetes changed capillary permeability in the pancreas permits the passage of trypsin

TABLE 8.—*Effect of p_H on Insulin Activity*

Amount	Before Injection	After Injection			
		1 Hour	2 Hours	3 Hours	
10 cc. of serum at p_H 7.4	96	72	70	76	
	98	80	75	80	
	90	85	75	78	
	92	84	75	75	
	85	75	75	70	
10 cc. of serum at p_H 8	98	85	74	78	
	96	85	65	58	
5 cc. of serum at p_H 7.4	92	70	55	55	
5 cc. of serum at p_H 8	96	68	65	62	
	96	60	60	60	
10 cc. of serum at p_H 6	110	48	40	..	Convulsions
	106	45	38	..	Convulsions
	80	50	40	30	Convulsions
	92	62	50	40	Convulsions
10 cc. of p_H 6 after incubation one hour at p_H 8	84	78	55	55	
10 cc. of saline at p_H 6	96	67	36	35	Convulsions
10 cc. of saline at p_H 7.4	102	58	42	30	
10 cc. of saline at p_H 8	104	62	40	26	
10 cc. of saline at p_H 8.2	94	35	40	..	Convulsions
10 cc. of saline at p_H 8.6	90	62	60	55	
	80	60	50	35	
10 cc. of saline at p_H 9.2	92	72	64	60	

into the blood stream, thus causing a comingling of the external and internal secretions of the pancreas. Epstein has shown that trypsin, in vitro, possesses power of rapidly neutralizing insulin under favorable conditions of hydrogen ion concentration.

In applying this idea here, we must assume that insulin inactivation by normal blood is due to trypsin, the concentration of which is increased in diabetes, thus accounting for the great inhibitory effect of the diabetic blood.

If we are to use Loewi's[6] work to explain our observation, a liver product or glycämin is present in diabetic blood which inactivates the

5. Epstein, A. A., and Rosenthal, N.: Am. J. Physiol. **70**:225, 1924; **71**: 316 (Jan.) 1925.

6. Loewi, O.: Klin. Wchnschr. **6**:2169 (Nov. 12) 1927.

insulin. Were that so, we would need another explanation for the inactivation of insulin by normal blood.

Collip [7] suggested that insulin needs a complement for its action. Lundsgaard,[8] Brugsch [9] and Ahlgren [10] have attempted to show that a coferment is necessary for insulin to be able to affect certain steps in carbohydrate metabolism. If we attempt to apply that conception, we should have to assume that the coferment or complement is inadequate

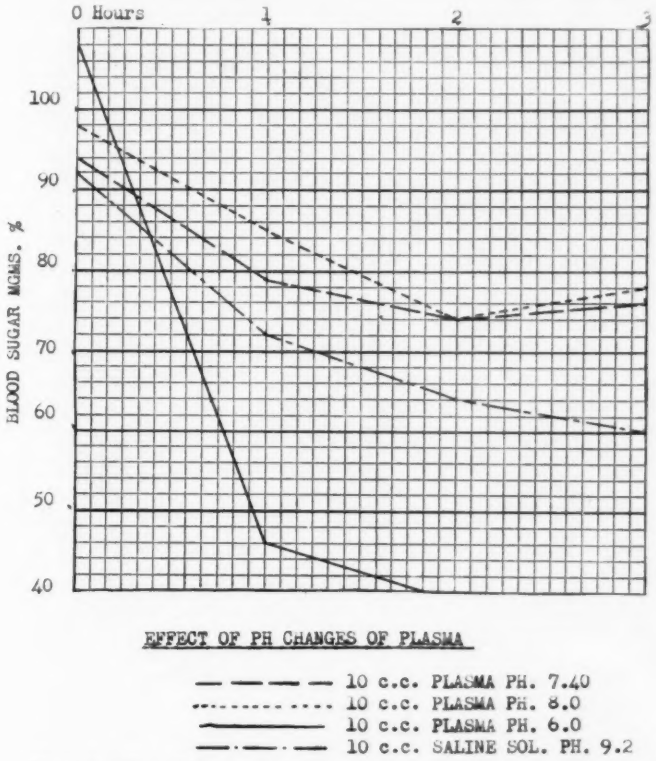

Chart 5.—The effect of p_H changes of plasma. The long dash line represents 10 cc. of plasma, with a p_H of 7.4; the short dash line, 10 cc. of plasma, with a p_H of 8; the continuous line, 10 cc. of plasma, with a p_H of 6, and the long dash dot line, 10 cc. of saline solution, with a p_H of 9.2.

7. Collip, J. B.: Am. J. Physiol. **63**:391, 1923.

8. Lundsgaard, C.; Holboll, S. A., and Gottschalk, A.: J. Biol. Chem. **70**: 89 (Sept.) 1926.

9. Brugsch, T., and Horsters, H.: Med. Klin. **22**:81 (Jan. 15) 1926.

10. Ahlgren, G.: Klin. Wchnschr. **3**:1158 (June) 1924; **3**:1222 (June) 1924.

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in normal blood in vitro and still less in diabetic blood or that conditions were not conducive for the coferment to function.

SUMMARY

We observed the following facts:

1. The blood plasma of a diabetic child who did not respond properly to insulin inhibited the insulin action in rabbits.

2. The same phenomenon occurred with blood from normal persons, young or old.

3. A greater inhibition was caused by blood cells than by plasma.

4. A still greater inhibition occurred when the cells were laked, which showed that the inhibiting substance is found mainly endocellular, and to a lesser degree in the plasma.

5. Greater inactivation is produced by the blood from diabetic patients than that resulting from the blood of normal persons.

6. We have control experiments to show that this inactivation is not due to dilution, viscosity of the fluid, rate of absorption from under the skin or adsorption by the cells, or the p_H of the blood for the period of incubation used in our experiments, not more than two hours, except at p_H 6 or lower when the inactivation ceases and at p_H 9.2 when it is increased, most likely due to the alkali itself.

The inhibition of the action of insulin by blood depends on the quantity of the active principle. That may explain why other authors who have used blood similarly obtained negative results. They probably used less blood per unit of insulin than we did. Furthermore, the inactivation may vary with different persons and with the same person at different times, perhaps even at different hours of the day, e. g., as related to meals, exercises and the like.

CHRONIC ULCERATIVE COLITIS

A REVIEW OF INVESTIGATIONS ON ETIOLOGY *

J. ARNOLD BARGEN, M.D.
ROCHESTER, MINN.

A symposium in 1928 on chronic ulcerative colitis in the Harvein Society of London reported in the *Lancet,* in which such eminent men as French, Tidy, Norbury, Smith, Wakely, Broadbent and Wilcox took part, added nothing to knowledge of the etiology of or treatment for this disease. The participants were convinced of the infectious nature of the disease and advocated irrigations and surgical procedures in the treatment. Later the editor of *Lancet* commented [1] on the unknown etiology of the disease. Therefore, this review seems opportune.

The voluminous literature on the subject of chronic ulcerative colitis is briefly summarized as follows: Wilks and Moxon [2] mentioned the disease in 1875 in their lectures on pathologic anatomy. A colored drawing by Cruveilhier,[3] including work reported between 1829 and 1842, presents a condition which certainly suggests chronic ulcerative colitis. Allchin, in 1885, exhibited to the London Pathological Society a specimen of a colon from a case of this disease, calling attention to features which he believed distinguished the condition as a disease entity. This was the first specimen of its kind brought before the society. White,[4] in 1888, gave a good pathologic description of the disease. Lockhart Mummery's [5] first description appeared in 1907 and 1908, and at this early date he emphasized the need of proctoscopic investigation, stressing the fact that knowledge before that time had been gathered chiefly from the patients' symptoms and from the postmortem examination. Allchin,[6] in 1909, wrote about the pathology and emphasized the

* Submitted for publication, Sept. 12, 1929.

* From the Division of Medicine, the Mayo Clinic.

1. Editorial: Ulcerative Colitis, Lancet **2**:78, 1928

2. Wilks, Samuel, and Moxon, Walter: Lectures on Pathological Anatomy, ed. 2, London, J. and A. Churchill, 1875.

3. Cruveilhier, Jean: Anatomie pathologique du corps humain ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible, Paris, 1829-1842, vol. 2, ch. 30.

4. White, W. H.: On Simple Ulcerative Colitis and Other Rare Intestinal Ulcers, Guy's Hosp. Rep. **45**:131, 1888.

5. Mummery, J. P. Lockhart: The Causes of Colitis with Special Reference to Its Surgical Treatment with an Account of Thirty-Six Cases, Lancet **1**:1638, 1907; Chronic Colitis and Its Surgical Treatment, Practitioner **1**:489, 1908.

6. Allchin, W. H.: Ulcerative Colitis, Proc. Roy. Soc. Med. **2**:59, 1909.

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unsatisfactory name of the disease. He made note of the fact that in twenty years prior to 1908, fifty-five patients with chronic ulcerative colitis had been admitted to Guy's Hospital, London. Hawkins,[7] in 1909, expressed the belief that "the pedigree of the disease can be traced to the bloody flux of Sydenham in 1669." Cameron and Rippmann,[8] in 1909 and 1910, reported statistics about the cases of this disease found in London hospitals from 1888 to 1910. Jex-Blake and Higgs[9] first spoke of its bacterial etiology in 1909, considering as factors, *Bacillus coli, Escherichia coli, Bacillus proteus-vulgaris, Bacillus pyocyaneus (Pseudomonas aeruginosa)* and streptococci. Wallis,[10] in 1909 reported streptococci in the stools of many of these patients and emphasized the significance of oral sepsis. White,[11] in 1911, noted that he "had met with cases due to *Bacillus coli* and pneumococci." Hutchison,[12] in 1911, wrote concerning the treatment of the disease, and commented on dietetic, medicinal and surgical measures. Lockhart Mummery,[13] in 1911, reported on its diagnosis with the sigmoidoscope. Lindenberg,[14] in 1912, advocated surgical treatment, describing colostomy as the procedure of choice. Wegele,[15] in 1913, stressed the seriousness of rectoscopy in these cases and commented on surgical and medical treatment. Kretschmer[16] also, in the same year, called attention to the exacerbations of the disease, and urged surgical procedure as a last resort. Lockhart Mummery,[17] in 1913, emphasized its serious nature by reporting a fatal case. Bassler,[18] in 1913, first suggested the significance of *Bacillus coli* in the condition.

7. Hawkins, H. P.: Natural History of Ulcerative Colitis and Its Bearing on Treatment, Brit. M. J. **1**:765, 1909.

8. Cameron, H. C., and Rippmann, C. H.: Statistics of Ulcerative Colitis from the London Hospitals: Guy's Hospital, Proc. Roy. Soc. Med. **2**:100, 1909; The Post-Mortem Statistics of Ulcerative Colitis at Guy's Hospital from 1888 to 1907, Guy's Hosp. Rep. **64**:353, 1910.

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16. Kretschmer, J.: Colitis ulcerosa, Centralbl. f. d. Grenzgeb. d. Med. u Chir. **17**:66, 1913.

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Little appeared in the literature from then until the statistical study of 117 cases by Logan,[24] in 1919. Logan expressed the belief that the basic etiologic factor was a metabolic disturbance. Lockhart Mummery,[25] in 1920, advocated surgical treatment, suggesting appendicostomy as the operation best fitted to the needs of this condition. He also emphasized the predominance of streptococci and bacilli of the colon group in stools of these patients and the absence of parasites. Hurst,[26] in 1921, expressed the belief that the condition was a postbacillary infection. Yeomans,[27] in 1921, found only the usual intestinal inhabitants by cultures of stools. Leusden,[28] in 1921, wrote of the significance of colon bacilli and dysentery bacilli. Bassler,[29] in 1922, again wrote of the significance of colon bacilli, asserting that this organism became virulent under certain conditions, and ventured the designation of

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28. Leusden, J. T.: Observations on Colitis Ulcerosa with a Contribution to the Knowledge of the Pathogenic Effects of Colon Bacilli, Nederl. Tijdschr. v. Geneesk. **65**:2890, 1921.

29. Bassler, Anthony: Treatment of Cases of Ulcerative Colitis, M. Rec. **101**:227, 1922.

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Bacillus pseudo-dysentericus coli. Rolleston,[30] in 1923, wrote of the significance of primary injury to the mucosa of the colon brought on by dietary or other deficiencies and at the taking on of pathogenic characteristics by the normal intestinal inhabitants. Hewes,[31] in 1923, wrote of the isolation of streptococci, staphylococci, colon bacilli and gas bacilli *(Clostridium welchii)* and emphasized the fact that often the disease appeared as a sequel to another infectious disease, such as pneumonia, influenza, measles or diphtheria. He stated that the infectious nature of the disease is undebatable. Stone,[32] in 1923, in advocating surgical treatment, found only the usual intestinal germs. Einhorn,[33] in 1923, in commenting on treatment, considered the dysentery bacilli as significant factors early in the disease. He did not doubt the infectious nature of the disease. Brown,[34] in 1923, commented on the enzymatic activity of the duodenal enzymes in cases of this disease. Logan,[35] in 1923, reported cure of the disease in three cases in which tincture of iodine was administered by mouth. Strauss, Friedman and Bloch,[36] in 1924, advocated colectomy for the condition and in commenting on etiology emphasized the predominance of streptococci in washings of the colon after ileostomy. Thorlakson,[37] in 1923, considered bacilli of dysentery as the original invaders in the disease but called attention to the fact that diplococci resembling pneumococci had been isolated in some of his cases in pure culture. He considered these as secondary invaders. About the time of these reports, the work to be reviewed here was under way, and the following historical facts ran contemporary with my studies.

Crohn and Rosenberg,[38] in 1924, advocated the use of acriflavine in irrigations of the colon in the treatment of this disease, and in 1925,

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31. Hewes, H. F.: Infectious Colitis, Boston M. & S. J. **188**:994, 1923.

32. Stone, H. B.: The Surgical Treatment of Chronic Ulcerative Colitis, Ann. Surg. **77**:293, 1923.

33. Einhorn, Max: Chronic Ulcerative Colitis and Its Treatment, New York M. J. **117**:214, 1923.

34. Brown, P. W.: Duodenal Enzymes in Chronic Ulcerative Colitis, M. Clin. N. Amer. **7**:97, 1923.

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49. Schur, H.: Ueber die Ursachen der Colitis Ulcerosa und Ihre Behandlung, Wien. klin. Wchnschr. **40**:756, 1927.

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experience and a comprehensive review of the literature. Wendkos,[50] of Philadelphia, and Soper,[51] of St. Louis, in 1927, reported on the use of the vaccine in the treatment of the disease and Chisholm,[52] of Denver, reported the same in 1928. Bassler,[53] in 1927, stated that the condition was an infectious disease entity but that he thought it was due to a variety of bacteria, including *Bacillus coli,* diplostreptococci, *Bacillus welchii* and *Bacillus pyocyaneus.* Jones,[54] in 1927, stressed the palliative effect of surgical measures on this disease. Torrey,[55] in 1927, stressed the etiologic significance of certain streptococci and diplostreptococci in the disease. Portis,[56] in 1927, made similar observations and advocated vaccine in treatment. Alekseiev,[57] of Russia, and Alessandri,[58] of Italy, in 1927, spoke of the infectious nature of chronic ulcerative colitis. Similarly, Bensaude and Oury,[59] of France, and Fenkner,[60] of Germany, in the same year, reported their belief in a bacterial etiology. Dustin,[61] in 1927, in a clinical report, considered the disease to be of an infectious nature. Brown,[62] as late as 1927, expressed the belief that "mucous," "catarrhal" and chronic ulcerative colitis were related conditions.

Crohn,[63] in 1929, reported that organisms of the streptococcus group were obtained by culture of the blood in two cases of severe ulcerative

50. Wendkos, S.: Chronic Ulcerative Colitis, M. J. & Rec. **125**:379, 1927.

51. Soper, H. W.: Chronic Ulcerative Colitis, Ann. Int. Med. **1**:313, 1927.

52. Chisholm, A. J.: Symptomatology and Treatment in Chronic Ulcerative Colitis, Colorado Med. **25**:28, 1928.

53. Bassler, Anthony: Ulcerative Colitis of So-Called Nonspecific Types, with Special Reference to Etiology, Pathology and Treatment, M. J. & Rec. **125**:253, 1927.

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61. Dustin, C. C.: Chronic Ulcerative Colitis, Rhode Island M. J. **10**:147, 1927.

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colitis. De Bere,[64] in 1928, isolated diplostreptococci from the rectal lesions, and by intravenous injection, he produced lesions similar to those in human beings. Garrett,[65] in 1928, observed the predominance of streptococci in cultures of stools of patients with colitis. Funkhouser,[66] in the same year, made similar observations; so also did MacNaughton [67] and Santee,[68] who stressed the probable significance of specific therapy. Horgan and Horgan,[69] in July, 1929, reviewed the facts of specific treatment and reported five cases in which the results from such treatment had been good.

The only recent article with a suggestion of other than infectious etiology is a report of five cases given by Larimore,[70] in 1928, before the American Gastro-Enterological Association. The patients in the five cases had been fed on foods presumably high in vitamins in an attempt at cure. He suggested the possibility that the syndrome was the result of a food deficiency.

From this chronologic historic survey of chronic ulcerative colitis, it becomes apparent that most men who come in contact with this condition think of it in terms of infection, that they are uncertain of the bacterium or bacteria guilty of the invasion, that dysentery bacilli, or closely allied forms and various forms of streptococci have received their share of blame, and that perhaps failure to find specific bacteria may have been dependent on methods employed in trying to isolate them.

REPORT OF STUDY

Many difficulties are encountered in studying the etiology of the disease by cultures of stools. By the ordinary cultural methods, I found that bacilli of the *Escherichia coli* group and various supposed saprophytes overgrew any other forms. Injections into animals of streptococci and other bacteria isolated from plates by the usual methods gave persistently negative results. It was thought that the causative organism might be sensitive to oxygen, that perhaps a medium affording a gradient of oxygen tension might serve to enhance the growth of this organism

64. De Bere, C. J.: Ulcerative Colitis, Read before the North Side Branch of the Chicago Medical Society, March 1, 1928.

65. Garrett, F. D.: Non-Specific Chronic Ulcerative Colitis, Southwestern Med. **12**:50, 1928.

66. Funkhouser, A. G.: Some Phases of Ulcerative Colitis, J. Indiana M. A. **21**:150, 1928.

67. MacNaughton, E.: Bacteriological Studies in Chronic Ulcerative Colitis, Canad. M. A. J. **18**:568, 1928.

68. Santee, H. E.: Ulcerative Colitis, Ann. Surg. **77**:704, 1928.

69. Horgan, Edmund, and Horgan, Joseph: Chronic Ulcerative Colitis; Results of Treatment with Vaccine in Five Cases, J. A. M. A. **93**:263 (July) 1929.

70. Larimore, J. W.: Chronic Ulcerative Colitis; Observations of Treatment by Diet, J. A. M. A. **90**:841 (March 17) 1928.

in advance of other bacteria, and that the organism of which the growth had been enhanced might localize in the colon by intravenous injection of the primary culture, just as Rosenow [71] has found to be the case in organisms obtained from patients with other diseases. A conveniently prepared medium which furnishes these requirements is Rosenow's dextrose brain broth.

If the results obtained were carefully checked against those obtained with ordinary mediums, such as Endo's medium, plain agar, dextrose broth and blood agar, it was thought that perhaps the causative organism or organisms might be singled out to the exclusion of other more saprophytic forms. Moreover, although the old method of stool culture might not yield the causative organisms, swabbings and scrapings from the bases of the ulcers, the surfaces of which first had been cleaned, or an attempt made actually to sterilize them, might be fruitful.

Method.—The following method was employed:

The rectum was thoroughly cleansed by repeated irrigations with warm water or solution of sodium chloride until the fluid returned clear. The patient was then placed over the Buie proctoscopic table, a sterile proctoscope or anoscope was inserted, and the surface thus exposed was thoroughly cleansed by swabbing the ulcers, or, if a particularly favorable place presented itself after the cleansing, it was swabbed with tincture of iodine. A sterile swab was then passed through the scope, and, by a twisting motion, some of the material from the base of an ulcer was drawn out and transferred immediately to warm dextrose brain broth. Or, if possible, a small Pasteur pipet was inserted instead of the swab and material was drawn out in this way. The material withdrawn was disposed of at once and in three ways: some was transferred to warm dextrose brain broth, some to warm physiologic solution of sodium chloride, and some, to glass slides for smears. The first was transferred to the incubator at once. The second was used for plating purposes, in shake cultures both of blood agar and of plain agar, and for streak plates of Endo's medium. Dilutions varied with specimens obtained, but it was soon learned that considerable dilution was necessary if one wanted individual colonies separated far enough so that they could be picked from twelve to eighteen hours later with a fine platinum wire. Smears of the third specimen, stained by Gram's method and carbol fuchsin, were examined for acid-fast bacilli and for the predominating bacteria. Stools previously had been examined for *Endamebas* and other parasites.

Diligent search for bacilli of dysentery was instituted, but without success. However, large numbers of gram-positive diplococci were found in smears from the lesions in the bowels of patients with chronic ulcerative colitis. The diplococci frequently were so numerous, particularly in smears of the more acute, more severe cases, that other bacteria were not seen.

The organisms also were found in predominating numbers in primary cultures in dextrose brain broth, the medium used by Rosenow and

71. Rosenow, E. C.: Studies on Elective Localization: Focal Infection with Special Reference to Oral Sepsis, J. Dent. Res. **1**:205, 1919.

others in studies on localization. It was believed, therefore, that growth of the causative organism might occur in this medium, since it afforded a gradient of oxygen tension, whereas only the more saprophytic organisms, or those not sensitive to oxygen, might develop on blood agar and in other ordinary mediums. Furthermore, localization in the colon might occur following intravenous injection of the primary mixed culture, and the causative organism might be isolated from the tissues of animals in which lesions developed. Thus, the animal would be used virtually as an artificial culture medium for selection of the organism that could do specific harm. Moreover, if pure cultures of the organism injected similarly after rapid subculture would produce similar lesions, such an organism could justly be considered as being a probable factor in the production of chronic ulcerative colitis. Positive results were established early in these investigations.

Healthy rabbits, weighing about 2 Kg., and free from diarrhea, as noted by several days' observation, were chosen. They were given greens, oats, hay and water, and were observed daily. Two or more rabbits received intravenous injection of cultures from each patient. In the earlier work from 2 to 5 cc. of a twenty-four hour dextrose brain broth culture, containing the diplococcus in predominance, was injected. Later from 3 to 12 cc. of a pure, rapidly isolated culture of the diplococcus was similarly injected. Rabbits that survived the inoculation were chloroformed for examination in from one to twenty-eight days, depending on the symptoms. Whether the rabbit died naturally or was chloroformed, at necropsy cultures were made from the blood, abdominal lymph nodes, spleen, and, in a few instances, from the lesions in the colon. Tissues were preserved in neutral formaldehyde for future examination or in Kaiserling's solution for museum purposes.

In smears from the lesions of patients, two organisms were seen: a gram-positive diplococcus and a gram-negative bacillus. In dextrose brain broth cultures made from the majority of the patients, the gram-positive diplococcus grew in predominance. On Endo's medium, a gram-negative bacillus grew, which in all essentials was like a colon bacillus. It was learned that at times, if tubes were heated slightly, gram-negative bacilli could be materially reduced in numbers, and often their growth could be inhibited completely.

The diplococcus did not grow on primary isolation on the surface of solid mediums, including blood agar, but after repeated subculture it grew characteristically as a fine colony on the surface. Furthermore, in shake culture it often appeared earlier in the depths of the medium.

As time went on, the technic adopted for cultivating material, obtained with sterile cotton swabs through the proctoscope from the bases of ulcers, was as follows:

Two cotton swabs that had been pressed against the bases of ulcers and rotated were placed immediately, one each in two tubes of dextrose brain broth, and were

incubated for from four to six hours. After from four to six hours, one set of three additional tubes of dextrose brain broth was inoculated with material from one of the original two tubes by simply shaking the swab into each of the three tubes of sterile dextrose brain broth. A second set of three tubes was similarly inoculated with material from the other of the original two tubes. One set of three tubes was heated for forty-five minutes at 55 C. and incubated; the other set of three tubes was incubated directly without heating. In eighteen hours, smears were made of the growth in each of the eight tubes of dextrose brain broth, the smears were stained by Gram's method, with safranine as a counterstain, and examined with the purpose of selecting the tube with the largest predominance of diplococci of the variety that is to be described. Subcultures of this were made on blood-agar plates. Cultures on Endo's medium and in dextrose broth had been made from the original swabs and were now examined. The growth here was predominantly, and usually, wholly of gram-negative bacilli, which by further study were found to belong to the *Escherichia coli* group.

The subculture for the first blood-agar plate was made by mixing one drop of inoculated dextrose brain broth from a capillary tube, with 10 cc. of physiologic solution of sodium chloride and one drop of this mixture, from a capillary tube, in 10 cc. of blood agar. Several dilutions were made from the subculture. These plates were incubated overnight.

The following morning colonies of diplococci were surrounded by a green zone, with a faintly hemolytic zone between the colony and the green zone. The colonies were picked with a platinum wire, were transferred to fresh tubes of dextrose brain broth and were incubated for eighteen hours. Smears of these were stained. The diplococci usually were rather closely fused in pairs, almost merging into a chain of four cocci. The organism so isolated has the following characteristics: It is lancet-shaped, slightly larger than a pneumococcus, gram-positive, and from early subculture, never appears in smears as more than two or four diplococci in a group. The appearance of its colony on blood agar is typical; so also is that on mannite agar, where it appears as a fine translucent colony, in striking contrast to the so-called enterococcus of Houston and McCloy,[72] which grows as a large white opalescent colony on this medium. The colony of *Streptococcus fecalis* appears much like that of the enterococcus. The diplococcus and enterococcus do not usually ferment mannite; *Streptococcus fecalis* does. The diplococcus does not ferment inulin; the *Diplococcus pneumoniae* does. The diplococcus ferments dextrose, lactose, saccharose, maltose, raffinose and salicin.

With full realization of the uncertain status of the so-called enterococcus in modern bacteriologic classifications, I am referring, when using this term, to the organism described by Houston and McCloy,[72] isolated by culture of stools from soldiers suffering from trench fever.

72. Houston, Thomas, and McCloy, J. M.: The Relation of the Enterococcus to "Trench Fever" and Allied Conditions, Lancet **2**:633, 1916.

He described an organism similar to or identical with *Micrococcus ovalis* of Escherich.[73] He isolated it by culture of stools in a great variety of conditions found during the war. He expressed the belief that it is "a constant inhabitant of the normal bowel. It differs from all other streptococci by the ease with which it grows on ordinary laboratory media and by its greater power of resistance; that is, cultures of it survive longer and are more difficult to kill. It grows well on all ordinary laboratory mediums under both aerobic and anaerobic conditions. On agar it forms a fine growth not unlike that of *Streptococcus pyogenes,* but the individual colonies are larger and more opaque. On gelatin at room temperature it forms a white growth in twenty-four hours and does not liquefy the medium. On Conradi-Drigalski's medium it grows well; in twenty-four hours the size of the individual colonies is intermediate between that of *Bacillus coli* and an ordinary streptococcus, and the medium becomes red. In broth the enterococcus grows well, producing a uniform turbidity and forming comparatively short chains and diplococci. It rapidly ferments dextrose, lactose, and saccharose, more slowly salicin; no change in mannite could be demonstrated in one week. Its resistance to heat is remarkable. A thick emulsion of the coccus in broth or physiologic solution of sodium chloride contained in a test tube was found in numerous experiments to be alive after an exposure for one and a half hours to a temperature of 55 C.

Other significant differences between the so-called enterococcus and the diplococcus of chronic ulcerative colitis are these: The diplococcus does not grow on plain agar, or only after repeated subculture and then sparingly; it does not grow on gelatin, and it does not coagulate milk.

To classify the organism of chronic ulcerative colitis one must take into consideration its tendency to form chains, after repeated subculture, its lack of power to ferment inulin, its green zone on blood agar, and its tendency to localize in tissues after intravenous inoculation, like other streptococci. It probably belongs to the streptococcus group, and the viridans species.

With this organism, rabbits have been immunized to produce a diagnostic serum. The diplococcus was grown in 100 cc. of 0.2 per cent dextrose broth for twenty-four hours. The broth culture was centrifugated, the supernatant fluid was decanted, and the precipitate was suspended in 100 cc. of physiologic solution of sodium chloride. This was preserved at the temperature of the icebox. Five tenths of a cubic centimeter of this suspension in solution of sodium chloride, was injected intravenously into a large rabbit; every two days another injection was made, and the amount was increased 0.5 cc. each time.

73. Escherich, T.: Die Darmbacterien des Neugeborenen und des Säuglings, Fortschr. d. Med. **3**:515 and 547, 1885.

When agglutination took place in dilutions well up between 1:1,000 and 1:10,000, which may occur in several weeks as determined by successive bleeding and titration of the serum, the intervals between injections were lengthened to once a week or once in ten days, which was sufficient to maintain the titer. As the work progressed, the other criterion by which identity of the diplococcus was established was determination of agglutinins and precipitins in the serums of these rabbits. The agglutination of the diplococcus in suspension in physiologic solution of sodium chloride usually occured in a dilution well above 1:1,000 and many times as high as 1:10,000.

Horses also were immunized by the methods of Rosenow,[71] and precipitins and agglutinins were determined with their serums.

In many of the rabbits given intravenous injections with the larger doses of the primary culture in dextrose brain broth, in which diplococci were the vastly predominating bacteria, or with the pure cultures made by rapid subculture of the original culture, severe diarrhea developed in from twenty-four hours to several days after the injections. Often there was blood and mucus in the stools. The rabbits lost weight and wasted rapidly.

In 189 cases (approximately 80 per cent) of chronic ulcerative colitis in which the patients were examined at the Mayo Clinic over a period of several years, the diplococcus was isolated in pure culture. With these strains, 459 healthy rabbits were given injections. Evidence of disease of the large intestine, from marked diarrhea with few, if any, hemorrhages, to extensive hemorrhages and severe ulceration with bloody discharges from the rectum, developed in 268 rabbits. The seat of election of these lesions corresponded rather accurately to that in the patients. Lesions, as a rule, were more extensive near the rectum and often involved only the distal half of the colon.

In a few instances, lesions occurred in other parts of the gastrointestinal tract in the form of submucous and disseminated hemorrhages. Rarely were lesions found in any other organs of the body.

Similar cultures were made in ninety-eight consecutive control cases in which proctoscopic examinations were made and in which the mucosa of the bowel was normal. Diplococci, in some essentials like those found in cases of chronic ulcerative colitis, were isolated from sixteen cases. Six of these strains were agglutinated by the immune horse serum used diagnostically and therapeutically; only four produced lesions in animals. These lesions were in the form of a few minute, disseminated hemorrhages in the colon. Other strains of streptococci were frequently isolated. None produced lesions in rabbits similar to those described.

Rosenow, Nickel, Meisser, Hufford, Cook and others, working along similar lines, with similar cultural methods in conditions other than

chronic ulcerative colitis, with other strains of streptococci, in the same laboratory, during the same period, with animals from the same common stock, induced lesions in the colon only in rare instances (not more than 2 per cent).

In twenty-one of twenty-five dogs which were given injections in a manner similar to that used in rabbits with from 3 to 15 cc. of a dextrose brain broth culture of the diplococcus, even more striking and more characteristic lesions of the colon occurred. In several dogs, bloody diarrhea was so severe that rectal prolapse occurred, providing ample opportunity to observe with the naked eye lesions like those seen with the proctoscope in human beings. Several other dogs were examined proctoscopically and the typical lesions observed.

An organism, in all essentials like the diplococcus described was isolated by blood culture from six patients with severe fulminating, acute ulcerative colitis. All these patients were acutely ill with a high septic type of fever, marked abdominal tenderness and extensive involvement of the colon. Three of the six patients died, and in two the organism was isolated at necropsy from the heart's blood. In sections through the lesions in the colon in these cases, and in sections through the ulcers in the colons of twelve other patients who died from chronic ulcerative colitis, large numbers of diplococci morphologically like those described were demonstrated in the depths of the inflammatory and granulation tissue. The Gram-Weigert method of staining of tissues for bacteria was used.

Another seemingly significant factor bearing on the causative relation of bacteria to this disease is the clinical observation that frequently tonsillectomy, removal of infected teeth or acute infections of the upper respiratory tract, cause marked acute temporary exacerbations of the disease. This suggests the presence of the causative bacteria in these foci.

Diplostreptococci, in all essentials like those isolated from the rectal lesions, have been isolated from periapical abscesses of teeth or from buried tonsillar abscesses, and cultures of these when injected intravenously have produced in animals lesions like those described. These organisms were agglutinated by the immune rabbit and horse serums. This has been the experience with the use of strains from many patients on several hundred rabbits.

Cook, working with Rosenow, has induced periapical infections at the apexes of teeth of a series of dogs by removing the pulp and inoculating the pulp canals with dense suspensions of diplococci isolated from the blood and mesenteric lymph nodes of rabbits in which hemorrhagic colitis developed following intravenous injection of diplococci which in turn had been isolated from the lesions or foci of patients with chronic ulcerative colitis. From eight to twelve months later, chronic

ulcerative colitis developed in a number of these dogs and was demonstrated proctoscopically and at necropsy.

Complications of chronic ulcerative colitis are multiple, and perirectal abscess is one of the more serious of them. On several occasions in localized perirectal abscesses which have occurred in the course of this disease, pure cultures of a diplostreptococcus have been isolated at the time of first drainage of the abscesses.

Finally, on the basis of the belief that these observations seem to establish this diplostreptococcus as significant in the etiology of chronic ulcerative colitis autogenous vaccines have been prepared and used as part of the treatment in the more chronic cases. Moreover, horses immunized by Rosenow with this organism have produced a serum of good titer, and this serum is being used in the treatment of patients with the more severe, acute cases. The results with these forms of treatment have given far better results than any form of treatment hitherto suggested. Approximately 70 per cent of patients have returned to normal, useful lives.

CONCLUSIONS

Chronic ulcerative colitis is an infectious disease involving primarily the colon. It has characteristic clinical, proctoscopic, pathologic and roentgenologic features.

A diplostreptococcus isolated from the lesions in the rectum, in distant foci, in the blood of the patients with the more acute stages of the disease, during life and after death, and demonstrated in the lesions in fatal cases has etiologic significance in chronic ulcerative colitis.

THE VALUE OF THE INDICAN DETERMINATION IN THE BLOOD IN CASES OF RENAL INSUFFICIENCY *

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The early recognition of functional impairment of the kidney, which will sooner or later terminate in uremia, is one of the most important problems in the diagnosis and treatment of the various forms of renal disease. Recent progress in chemical analysis of the blood has been great, particularly with regard to the accumulation of nitrogen waste products as a sign of renal insufficiency. Yet often one will be disappointed in diagnosis and prognosis if too much stress is laid on the nonprotein nitrogen, the urea nitrogen, the uric acid or the creatinine readings of the blood.

For one may find excessive amounts of these substances in patients who die of myocardial insufficiency, and in whom, apart from passive congestion, the kidneys show no anatomic changes. If such patients recover, improvement of the function of the heart also quickly ameliorates the chemical condition of the blood. In cases of pneumonia or other infections or in cachectic states of varied cause one may be similarly misled. On the other hand, considerable renal parenchyma can be destroyed without markedly affecting the urea, the uric acid or the creatinine content of the blood. Accumulation of nitrogen waste products may appear very late and to limited degree, yet the patient soon dies of uremia.

In addition to the nitrogenous substances mentioned, indican has repeatedly been suggested as a sensitive indicator of renal insufficiency. This indicator is said to have the advantage of detecting the seriousness of the conditions at a time when the other substances of the blood are still within normal limits. The appearance of indican seems to be dependent only on the functional state of the renal parenchyma, and is little if at all influenced by mere congestion of the kidney or by nonrenal conditions. Its appearance is conclusive evidence of an impending and fatal insufficiency of the kidneys, that is, of uremia.

Indican is derived from indole, which is formed by putrefaction in the intestine from aromatic radicals of the proteins. Indole is absorbed

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* From the Uihlein Memorial Laboratory of the Grant Hospital and the Department of Pathology of the Cook County Hospital.

from the intestinal tract, and in passing through the body is oxidized to indoxyl. In the liver, indoxyl unites with sulphuric and glycuronic acid. Indican is the potassium salt of the indoxyl-sulphuric acid. With normal kidneys, it is promptly excreted by them even if excessive amounts of indole are formed in the intestine. With the earliest absolute impairment of the renal parenchyma, the kidneys become unable to excrete the amount of indican normally formed. Its excretion is stopped even when urea nitrogen and creatinine are still passed through. It ceases to appear in the urine and accumulates in the blood.

Obermeyer and Popper, in 1911, were the first to demonstrate the indicanemia of uremia. They used the same method which is applied to the urine (ferric chloride-hydrochloric acid test). Jolles modified this method, making it much more sensitive, so that the determination of indican in the blood was placed on a quantitative basis as accurate as the creatinine or urea nitrogen readings. With the Jolles modification, the indoxyl is transformed into indigolignon, which because of its intense violet coloration can be detected in the faintest traces. With the aid of this highly sensitive test, Haas was able to detect traces of indican even in the blood of normal persons. Values of 0.2 mg. per hundred cubic centimeters of blood, or more, are abnormal and indicate a renal insufficiency. Baar found that in cases of uremia the indican may rise to 3 and even to 10 mg. per hundred cubic centimeters. The great value of the determination of blood indican in renal disorders was confirmed by several investigators, notably Umber and Rosenberg, Schilling, Eufinger, Mute, Baar and Krokiewicz.

Thus far, no work on indicanemia has been done in this country or in Great Britain. It is our purpose in this paper to call attention to this method, which, in our hands, has proved satisfactory.

DETERMINATION OF INDICAN IN THE BLOOD

Either oxalated plasma or serum may be used. Plasma has the advantage that one need not wait for the clot to separate from the serum, and in that it can be taken from the samples already collected for the determination of the nonprotein nitrogen, urea nitrogen and creatinine. However, it is essential to use lithium oxalate, since potassium oxalate seems to interfere with the color reaction (as it does also in the determination of uric acid). Serum has the advantage that no special lithium oxalate bottles are required. The blood sample may be placed in any available tube.

The following reagents are required: (1) 20 per cent trichloracetic acid; (2) 5 per cent alcoholic solution of thymol; (3) concentrated fuming hydrochloric acid (clinically pure, specific gravity, 1.19), containing 0.5 per cent ferric chloride; (4) chloroform (Merck's reagent, chemically pure), and (5) distilled water.

The following apparatus is required: (1) a 100 cc. graduated cylinder, preferably with glass stopper; (2) an Erlenmeyer flask, of about a 200 cc. capacity, and (3) a filter funnel.

Quantities may be measured either gravimetrically or volumetrically. Five grams or cubic centimeters of the separated plasma or serum is placed in an Erlenmeyer flask. An equal amount of distilled water is added. The mixture is precipitated by adding an equal quantity, i.e., 10 Gm. or cc., of the trichloracectic acid. The flask is then rotated for about two minutes. After five minutes the contents are filtered into the graduated cylinder. Through a capillary pipet, 10 drops of the thymol solution are added to the clear filtrate. Then is added an amount of the hydrochloric acid-ferric chloride solution equal to that of the filtrate obtained. The mixture is shaken well and allowed to stand for two hours. Then 5 cc. of chloroform is added, and the mixture is shaken for two or three minutes and allowed to stand. The chloroform dissolves out the indigo and promptly settles to the bottom.

For accurate, quantitative readings, the chloroform is pipetted off, and the intensity of its coloration is compared with an artificial or natural standard solution. A Dubosque or Autenrieth colorimeter is used for this purpose.

Preparation of the Natural Standard.—Three milligrams of indican is dissolved in 30 cc. of chloroform, and placed in a graduated glass cylinder. To this solution is added 30 cc. of a 0.5 per cent solution of ferric chloride in concentrated hydrochloric acid, and 30 capillary drops of a 5 per cent alcoholic thymol solution. The mixture is shaken well and left standing for two hours. The colored chloroform is pipetted off, and the remaining solution is shaken with another 10 cc. of chloroform which is added to the portion previously removed. This procedure is repeated until the total amount of chloroform is 60 cc. This 60 cc. contains 3 mg. of indican; 10 cc. contains 0.5 mg., or 100 cc. contains 5 mg. By using this chloroform solution as the standard, the calculation of the unknown quantity is done as follows:

$$\frac{\text{Reading of the standard} \times 0.5}{\text{Reading of the unknown} \times 10} = \text{milligrams of indican per hundred cubic centimeters of blood.}$$

If the coloration of the standard is too intensive, further dilutions may be made with chloroform. Of course, these dilutions are taken into consideration in calculating the unknown quantity.

Preparation of the Artificial Standard.—Indican cannot be obtained on the market. It is cumbersome to prepare and requires special technical skill and laboratory facilities. Prof. Dr. F. Silberstein of the Institute of Experimental Pathology of the University of Vienna supplied us with a quantity of indican sufficient to prepare a natural standard. The necessity of preparing an artificial standard has been recognized by earlier investigators. Thus, Erick suggested a mixture of scarlet red and eriglaucin (Gruebler). For our artificial standard, we selected two dyes which are found in every laboratory, namely, eosin (water soluble, yellow) and gentian violet. The artificial standard consists of 6 capillary drops of a 1 per cent solution of gentian violet in water, 3 drops of a 1 per cent solution of eosin in water, 10 cc. of 94 per cent alcohol and 30 cc. of distilled water. This mixture corresponds in tint and intensity to the original standard of 5 mg. of indican in 100 cc. of chloroform. From the stock solution, various dilutions may be made, water being used as a diluent. Besides being easily obtainable, this artificial standard has the advantage of not fading. The higher dilutions of the natural standard fade with time.

To facilitate the dilutions of the standards, the accompanying tables are given.

Simplification of the Method for Use by the Practitioner.—The use of either of these standards firmly establishes the determination of indicanemia as a quanti-

tative laboratory method that is as accurate as the urea nitrogen or creatinine readings. But laboratory facilities are not always available in the stress of practice. Diagnosis and prognosis often cannot wait on a report of the chemistry. Further, the expense of any determination of blood chemistry may be a burden to the patient. We have therefore attempted to simplify the determination of indacanemia so that it may be performed by the practitioner in his own office with a minimum of time and effort and with an accuracy sufficient for his immediate needs.

For this purpose, the test is given just as described. Volumetric quantities are usually easier to follow. No standards or colorimeter are required. When the chloroform settles to the bottom of the graduated cylinder in which it has been

TABLE 1.—*(Standard 1) Dilutions of Standard Solutions with Equivalents of Indican*

Amounts of Stock Solution, Cc.*	Amount of Chloroform Added, Cc.	Equivalent of Indican, Mg.†	Index of Intensity of Indican
10	0	0.5	
9	1	0.45	4+
8	2	0.40	
7	3	0.35	
6	4	0.30	3+
5	5	0.25	
4	6	0.20	
3	7	0.15	2+
2	8	0.10	

* Stock solutions of smaller amounts may be used.
† One hundred cubic centimeters of the stock solution corresponds to 5 mg. of indican.

TABLE 2.—*(Standard 2) Dilutions of Standard Solutions with Equivalents of Indican*

Amount of Stock Solution, Cc.*	Amount of Chloroform Added, Cc.	Equivalent of Indican, Mg.†	Index of Intensity of Indican
10	0	0.05	
9	1	0.045	1+
8	2	0.040	
7	3	0.035	
6	4	0.030	Trace
5	5	0.025	
4	6	0.020	
3	7	0.015	
2	8	0.010	Negative
1	9	0.005	

* Stock solutions of smaller amounts may be used. Solutions may be prepared from the artificial stock standard (10 cc. or 0.5 mg. of indican) in the same way as the natural standard solutions, water being used as a diluent.
† One hundred cubic centimeters of the stock solution corresponds to 0.5 mg. of indican.

shaken, it is directly observed. If it is a deep blue, marked indicanemia is present and the patient will die in uremia. If it is colorless or only faintly blue, there is no significant indicanemia and consequently no uremia. Intermediate or doubtful color reactions are not often encountered. When they occur, they have the same significance as an intermediate elevation of urea nitrogen: i. e., the patient bears watching. A practical makeshift standard may be found in the ordinary Dunning colorimeter used for tests of phenolsulphonphthalein excretion. A color corresponding to 40 or above on the Dunning colorimeter is the indication of a grave indicanemia; one below 15 shows a negligible degree. The entire test requires about ten minutes and but a few simple pieces of apparatus. In two hours the determination is available for reading and for clinical use.

TABLE 3.—*Marked Indicanemia, Showing High Urea Nitrogen Values; Death in Uremia*

No.; Patient	Race, Sex and Age	Clinical Diagnosis	Blood Chemistry				Cause of Death	Date, 1929	Postmortem Data When Autopsy Was Permitted
			Date, 1929	Urea Nitrogen, Mg. per 100 Cc. of Blood	Creatinine	Indican +			
1 V. F.	Colored Male 52	Chronic diffuse nephritis	3/20	139.6	13.3	4	Uremia	3/24	Chronic glomerulonephritis, the extracapillary form
2 L. R.	Colored Female 33	Chronic diffuse nephritis	3/16	144.7	8.0	4	Uremia	3/12	
3 J. C.	White Male 48	Chronic diffuse nephritis	3/13/	132.6	9.2	4	Uremia	3/14	
4 I. W.	Colored Female 50	Chronic diffuse nephritis	3/18	173.0	12.0	4	Uremia	3/21	(P.M. 250) Primary contracted kidney; malignant renal arteriosclerosis; uremic colitis
5 H. E.	White Male 32	Chronic diffuse nephritis	5/ 2	108.0	9.3	4	Uremia	5/ 6	
6 R. T.	Colored Male 36	Chronic diffuse nephritis	5/28	172.0	15.5	4	Uremia	3/29	(P.M. 450) Chronic glomerulonephritis
7 N. R.	Colored Male 32	Chronic diffuse nephritis	4/16	100.0	10.0	4	Uremia	4/22	(P.M. 340) Primary contracted kidney; malignant renal arteriosclerosis; uremic colitis
8 C. H.	Colored Male 39	Chronic diffuse nephritis	4/16	102.7	12.0	4	Uremia	4/18	
9 P. H.	Colored Male 59	Chronic diffuse nephritis	5/ 6	107.2	6.7	4	Uremia	5/ 9	(P.M. 394) Primary contracted kidney; malignant renal arterio sclerosis
10 T. N.	Colored Male 24	Chronic diffuse nephritis	6/15	120.0	13.0	4	Uremia	6/17	
11 P. B.	White Female 45	Chronic diffuse nephritis	6/24	120.0	9.2	4	Uremia	6/28	
12 L. N.	White Female 32	Chronic diffuse nephritis	3/ 4 3/18	72.0 145.7	6.5 10.9	4 4	Uremia Uremia	3/13	
13 J. B.	Colored Male 47	Chronic diffuse nephritis	4/25 5/ 6	103.0 170.0	11.0 12.0	4 4	Uremia Uremia	5/ 7	
14 C. D.	Colored Male 20	Chronic diffuse nephritis	5/ 4	84.0	13.3	4	Uremia	5/ 7	
15 S. B.	White Male 27	Subchronic diffuse nephritis	6/15	124.0	8.3	4	Uremia	6/17	
16 L. P.	Colored Female 44	Primary contracted kidney	3/30	107.0	9.3	4	Uremia	4/ 3	
17 L. D.	Colored Male 30	Chronic pyelonephritis	5/ 3	84.0	10.0	4	Uremia	5/ 4	(P.M. 462) Chronic pyelonephritis with marked reduction of the renal parenchyma
18 T. W.	White male 78	Pyelonephritis	6/20	80.0	8.0	4	Uremia	6/24	
19 W. B.	Colored Male 54	Urinary retention from a gonorrheal ureteral stricture	3/27	78.0	7.0	4	Uremia	3/30	
20 G. B.	White Male 67	Hypertrophied prostate	5/ 6	73.0	5.0	3	Uremia	5/10	

OBSERVATIONS

To establish the reliability and clinical value of this chemical analysis of the blood for indican, 104 cases were picked at random. The observations on indican and their implication with respect to renal insufficiency were compared with those of the urea nitrogen and creatinine readings. Special stress was laid not only on the clinical diagnosis, but on the ultimate fate of the patients and, if permission could be

TABLE 3.—*Marked Indicanemia, Showing High Urea Nitrogen Values; Death in Uremia—Continued*

No.; Patient	Race, Sex and Age	Clinical Diagnosis	Blood Chemistry: Date, 1929	Urea Nitrogen Mg. per 100 Cc. of Blood	Creatinine	Indican +	Cause of Death	Date, 1929	Postmortem Data When Autopsy Was Permitted
21 B. B.	Colored Female 52	Primary contracted kidney	4/16	64.0	8.0	4	Uremia	4/27	
22 C. B.	White Male 25	Chronic diffuse nephritis	4/17	51.0	6.0	4	Uremia	4/18	(P.M. 323) Chronic glomerulonephritis; uremic colitis
23 M. M.	White Male 23	Chronic diffuse nephritis	3/11	38.8	2.6	4	Uremia	3/26	
24 R. N.	White Male 45	Chronic diffuse nephritis	3/13	56.0	4.6	4	Uremia	3.20	
25 L. L.	White Female 15	Chronic diffuse nephritis	4/20	45.0	3.0	3	Uremia	5/ 7	
26 M. C.	Colored Female 48	Chronic diffuse nephritis	4/ 7 5/ 1 5/ 7 5/ 8	50.0 70.0 50.0 44.0	3.0 7.5 3.0 2.8	4 4 4 4	Uremia Uremia	 5/ 8	
27 M. S.	Colored Female 38	Chronic diffuse nephritis	4/20	42.0	3.0	4	Uremia	5/20	
28 A. J.	Colored Male 33	Chronic diffuse nephritis	4/11	47.0	3.5	4	Uremia	5/25	
29 C. H.	White Male 27	Tuberculous pyelonephritis	3/13	48.0	3.3	4	Uremia	4/28	
30 F. B.	White Male 60	Generalized tuberculosis	4/16	60.0	4.3	4	Uremia	4/18	(P.M. 336) Primary contracted kidney; malignant renal arteriosclerosis; tuberculous peritonitis
31 D. C.	White Male 50	Primary contracted kidney	3/20	53.0	6.6	4	Uremia	4/ 1	

obtained, on observations at autopsy. The cases were divided into four groups, according to the amount of indican in the blood.

Group 1 comprises the cases with the most intensive indicanemia, showing a range of indican from 2.5 to 5.0 mg. per hundred cubic centimeters of blood. (Excessive values of 10 mg. and over, as described by other investigators, were not encountered by us.) The degree of retention is expressed in + signs; + 3 means from 2.5 to

TABLE 4.—*Absent or Faint Indicanemia, with Low or Moderate Urea Nitrogen Values; Death from Other Causes than Uremia*

No.; Patient	Race, Sex and Age	Clinical Diagnosis	Blood Chemistry: Date, 1929	Blood Chemistry: Urea Nitrogen, Mg. per 100 Cc. of Blood	Blood Chemistry: Creatinine	Blood Chemistry: Indican	Cause of Death	Postmortem Data
32 M. B.	Colored Female 36	Hypertensive disease of the heart	4/ 3	34.0	2.2	0	Cardiac decompensation	
33 J. B.	White Male 76	Hypertensive disease of the heart	2/26	26.0	2.0	0	Cardiac decompensation	
34 S. M.	White Male 46	Hypertensive disease of the heart	2/27	18.7	...	+	Cardiac decompensation	
35 A. M.	White Female 71	Hypertensive disease of the heart	4/27	40.0	2.3	+	Cardiac decompensation	
36 C. W.	Colored Female 33	Chronic diffuse nephritis	4/15	28.0	2.0	+	Cardiac decompensation	
37 N. H.	White Female 90	Chronic diffuse nephritis	4/ 2	28.0	2.0	0	Cardiac decompensation	
38 C. M.	Colored Male 49	Syphilitic disease of the heart	3/18	30.0	2.0	0	Peritonitis	(P.M. 247) Diffuse peritonitis following perforated empyema of the appendix
39 J. H.	Colored Male 56	Hypertensive disease of the heart	2/25	32.0	3.0	+	Hemorrhage from bleeding peptic ulcer	
40 C. J.	White Male 53	Hypertensive disease of the heart	4/16	23.0	1.9	+	Hemorrhage from bleeding peptic ulcer	(P.M. 349) Chronic gastric ulcer with exposed and opened artery in its base
31 A. W.	Colored Female 48	Hypertensive disease of the heart	3/29	23.6	2.3	+	Pneumonia	
42 L. D.	White Male 65	Hypertrophied prostate	3/12	43.0	3.0	0	Cardiac decompensation	
43 J. W.	Colored Male 35	Severe burns with hematuria	3/ 1	12.0	...	0	Burn shock	
44 W. W.	Colored Male 38	Syphilitic disease of the heart	3/19	25.7	1.8	0	Pneumonia	
45 P. H.	White Female 71	Uremia	5/24	15.0	1.4	0	Cerebral thrombosis	(P.M. 442) Cerebral hemorrhage
46 J. K.	White Female 36	Chronic diffuse nephritis	3/10	17.0	1.7	+	Pneumonia	
47 G. M.	Colored Male 51	Pulmonary tuberculosis	2/25	41.0	...	0	Pulmonary tuberculosis	(P.M. 470) Fibrocaseous, acino-nodose tuberculosis of the lungs
48 B. P.	White Female 12	Septic meningitis	4/ 4	41.0	2.1	0	Septic meningitis	
49 A. A.	White Male 55	Carcinoma of the gallbladder	4/ 3	44.0	2.3	0	Cachexia	
50 W. K.	White Male 49	Scurvy	2/28	45.0	2.6	0	Scurvy	

3.5 mg. per hundred cubic centimeters of blood and + 4 means from 3.6 to 5 mg. These cases would present a deep purple color in the test for indican, and the value would correspond to 40 or above on the Dunning

TABLE 5.—*Absent or Faint Indicanemia, with Marked Increase of Urea Nitrogen; Death from Causes Other Than Uremia*

			Blood Chemistry					
				Urea Nitrogen, Mg. per 100 Cc.				
No.: Patient	Race, Sex and Age	Clinical Diagnosis	Date, 1929	of Blood	Creatinine	Indican	Cause of Death	Postmortem Data
51 J. M.	White Male 54	Hypertensive disease of the heart	6/28	45.0	3.8	+	Cardiac decompensation	(P.M. 496) Eccentric hypertrophy of the heart; chronic passive congestion
52 F. F.	White Female 35	Uremia	6/22	45.0	3.2	0	Pneumonia	
53 N. T.	White Female 75	Chronic myocarditis	2/25	70.0	...	+	Cardiac decompensation	P.M. A case for the coroner; chronic myocarditis; no renal damage
54 R. L.	White Male 64	Hypertrophied prostate	4/ 1 4/ 3	28.5 59.0	3.3 ...	0 0	Postoperative bronchopneumonia	
55 R. A.	White Male 65	Hypertrophied prostate	3/16 3/19 3/25	75.0 60.0 58.0	5.0 3.7 3.4	+ + +	Postoperative cardiac decompensation	
56 W. J.	White Male 70	Carcinoma of prostate	2/ 8	52.0	3.0	0	Pneumonia	
57 J. M.	White Female 40	Primary anemia	6/24	82.0	4.8	+	Primary anemia	(P.M. .95) postpurperal sepsis and secondary anemia
58 K. H.	White Male 55	Stone in the bladder	3/ 4	73.0	5.0	+	Postoperative cardiac decompensation	
59 H. C.	White Male 54	Urinary retention	2/26	50.0	...	+	Cardiac decompensation	
60 J. P.	White Male 47	Exophthalmic goiter	2/ 9 2/25	20.0 71.0	... 5.1	0 +	Thyroid crisis	
61 V. B.	White Male 59	Carcinoma of the gallbladder	3/ 5	64.4	...	+	Cachexia	(P.M. 204) Carcinoma of the gallbladder
62 F. H.	White Male 61	Penumonia	3/12	49.0	3.3	0	Pneumonia	
63 G. D.	White Male 45	Uremia	6/ 8	51.0	3.0	0	Pneumonia	(P.M. 476) Bronchopneumonia
64 G. L.	Colored Male 53	Hypertensive disease of the heart	5/20 6/24	9.3 72.0	... 4.0	0 +	Cardiac decompensation	
65 R. R.	Colored Male 45	Hypertensive disease of the heart	3/29	53.0	4.9	0	Cardiac decompensation	

colorimeter. The values for urea nitrogen in this group of patients with marked indicanemia varied from 38.8 to 173 mg. per hundred cubic centimeters and that for creatinine from 2.6 to 15.5 per hundred cubic centimeters of blood.

All of the thirty-one patients in this group showed a marked indicanemia. All died in uremia. Most of them had also marked retentions of nitrogen. But in some (cases 23, 25, 27, 28 and 29) the urea nitrogen and the creatinine were only slightly increased and would not have indicated the presence of grave renal insufficiency. Yet in these the marked accumulation of indican proved more reliable, for these patients died in uremia, despite the low blood nitrogen. It was further shown that the indican reaction announced the imminent danger earlier, was more sensitive to absolute renal insufficiency, than the two other determinations (case 26).

As to clinical diagnosis, these cases included seventeen of chronic diffuse glomerulonephritis, seven of malignant renal sclerosis (primary contracted kidney), two of subacuate glomerulonephritis and three of pyelonephritis, hypertrophied prostate and gonorrheal urethral stricture with urinary retention. No case of acute glomerulonephritis was encountered in this group.

In the second group are collected cases which showed no rise or but a slight rise of the blood indican. The reading was between 0.05 and 0.35 mg. per hundred cubic centimeters of blood. In the literature, from 0.05 to 0.15 mg. per hundred cubic centimeters are given as the normal values. The symbol O includes the cases showing from 0.05 to 0.15 mg. and + the cases showing from 0.2 to 0.35 mg. They would correspond to a colorless or faintly purple coloration of the chloroform, to a reading of 15 or less on the Dunning colorimeter. In this group, the urea nitrogen varied from 12.0 to 82 mg. per hundred cubic centimeters of blood, and the creatinine from 1.4 to 5.1 mg.

The thirty-four patients in this group showed an absence of, or a faint, indicanemia. Among these there were eleven (table 5) with high values for urea nitrogen and creatinine, values which would have suggested uremia. Despite this, there was no case of nephritis or other grave renal involvement in this group, and none of the patients died of uremia. The clinical diagnosis and the cause of death as determined independently, with no reference to the observations on indican, are evident from the lists given. Thus, in nonuremic, as well as in uremic conditions, the indican determination surpasses in reliability the blood analysis for urea nitrogen and creatinine.

In group 3, the urea nitrogen values varied from 9.8 to 84 and the creatinine from 1.8 to 8.5 mg. per hundred cubic centimeters of blood. Yet in all these thirty-two patients, the blood indican was normal or but negligibly elevated, and all thirty-two left the hospital markedly improved or completely recovered.

In this "recovery group," the discrepancy between the results of the indican and of the urea nitrogen and creatinine determinations is still more striking than it is in group 2. There were six patients (cases

TABLE 6.—*Absent or Faint Indicanemia with Low or Moderate Urea Nitrogen Values: Recovery*

No.; Patient	Race and Sex	Age	Clinical Diagnosis	Blood Chemistry				Result
				Date, 1929	Urea, Nitrogen Mg. per 100 Cc. of Blood	Creatinine	Indican	
66 R. O.	Colored Male	56	Hypertensive disease of the heart	4/15	19.6	1.75	+	Recovery
67 W. C.	White Male	65	Hypertensive disease of the heart	6/ 1	23.0	1.9	0	Recovery
68 L. O.	White Male	55	Hypertensive disease of the heart	3/29 4/ 4	32.0 45.0	2.5 ...	0 0	Recovery Recovery
69 J. L.	White Male	50	Hypertensive disease of the heart	4/ 4	31.0	2.1	+	Recovery
70 O. P.	White Male	51	Hypertensive disease of the heart, with benign renal arteriosclerosis	2 25	23.0	1.8	0	Recovery
71 N. B.	White Male	49	Hyptertensive disease of the heart, with benign renal arteriosclerosis	3/ 5	30.0	2.2	..	Recovery
72 A. J.	White Male	80	Hypertensive disease of the heart, with benign renal arteriosclerosis	4/ 2	23.0	1.8	0	Recovery
73 A. S.	White Male	82	Hypertensive disease of the heart, with benign renal arteriosclerosis	2/ 3	33.0	2.0	..	Recovery
74 J. M.	White Male	59	Hypertensive disease of the heart, with benign renal arteriosclerosis	3/13	9.8	...	0	Recovery
75 D. H.	Colored Male	54	Hypertensive disease of the heart, with benign renal arteriosclerosis	3/27	32.7	2.1	0	Recovery
76 N. V.	White Female	39	Syphilitic disease of the heart	3/29	23.0	1.9	0	Recovery
77 E. M.	Colored Female	13	Acute nephritis	3/ 3	9.8	...	0	Recovery
78 W. P.	Colored Male	15	Subacute nephritis	4/15	24.0	2.0	0	Recovery
79 I. M.	White Female	41	Chronic diffuse nephritis....	4/18	37.0	2.5	0	Recovery
80 M. S.	White Female	48	Chronic diffuse nephritis.....	5/21	17.0	...	0	Recovery
81 J. O.	Colored Male	38	Urinary extravasation from a gonorrheal urethral stricture	3/30	29.0	2.0	0	Recovery
82 G. O.	White Male	53	Hypertrophied prostate	3/12	41.0	2.7	..	Recovery
83 G. F.	White Male	75	Hypertrophied prostate	4/22	32.7	2.1	..	Recovery
84 J. D.	White Male	71	Carcinoma of the prostate..	4/12	39.0	3.0	0	On deep roentgen therapy
85 A. T.	White Male	49	Carcinoma of the urinary bladder	4/ 2	34.5	2.2	0	On deep roentgen therapy
86 O. K.	White Male	45	Chronic alcoholism	3/25	28.0	2.2	0	Recovery
87 A. R.	White Male	46	Chronic alcoholism	4/22	46.0	2.9	..	Recovery
88 E. G.	White Female	68	Chronic arthritis	3/26	42.0	2.8	0	Recovery
89 W. S.	White Male	59	Serum sickness	4/ 1	28.5	2.1	0	Recovery
90 E. B.	White Male	39	Chronic bronchitis	3/21	39.7	2.5	0	Recovery

91 to 97) with high urea nitrogen and creatinine values. Yet in these, indicanemia was absent and the patients recovered.

In group 4 are collected the few cases in which the results of the indican determination was doubtful. The readings varied from 1 to 2 mg. per hundred cubic centimeters of blood, a + 2 reaction. This would correspond to an intermediate reaction, a distinct but slight purple discoloration of the chloroform, from 15 to 30 on the Dunning colorimeter. An elevation of urea nitrogen to 30 or 40 mg. would be no more determinate. In these cases a repetition of the test a few days or weeks later yielded the decision. Either the indican went up and the patient died from uremia; or the value remained stationary and

TABLE 7.—*Absent or Faint Indicanemia, with High Urea Nitrogen; Recovery*

No.; Patient	Race and Sex	Age	Clinical Diagnosis	Blood Chemistry: Date, 1929	Urea Nitrogen Mg. per 100 Cc. of Blood	Creatinine	Indican	Result
91 R. N.	White Male	54	Hypertensive disease of the heart; benign renal arteriosclerosis	3/1	62.5	5.0	0	Recovery
92 S. S.	Colored Male	46	Syphilitic disease of the heart	4/27	58.0	4.8	0	Recovery
93 B. S.	White Male	21	Chronic diffuse nephritis....	3/25	50.0	...	0	Recovery
94 R. M.	White Female	29	Acute hemorrhagic nephritis..	4/18	84.0	8.5	0	Recovery
95 M. R.	White Male	63	Hypertrophied prostate	3/27	52.3	2.5	0	Recovery
96 C. M.	White Male	65	Chronic alcoholism	4/27	54.0	3.7	0	Recovery
97 C. C.	Colored Female	23	Stomatitis	4/12	55.5	...	0	Recovery

death from cardiac decompensation or bronchopneumonia terminated the case; or the indican went down and the patient recovered.

CONCLUSIONS

In our series of one hundred and four cases, there was not a single one in which a marked accumulation of indican in the blood (+ 3 and + 4, corresponding to 2.5 to 5.0 mg. per hundred cubic centimeters) failed to announce an approaching uremia or one already present. Were the urea nitrogen and creatinine high or low, a marked indicanemia spelled death in uremia. On the other hand, if the indican reaction were weak or absent, then even in spite of a high urea nitrogen and creatinine value there was no danger of uremia. The patient recovered, or if not, died of myocardial insufficiency, pneumonia, cerebral hemorrhage or any other condition than uremia. We may conclude, then, from this work that the determination of indican in the blood is a sensitive and

specific test of absolute renal insufficiency, that is reliable in diagnosis and in prognosis.

By use of the standards described, indican determinations are established as a quantitative laboratory procedure that is as accurate as the urea nitrogen or creatinine readings. A simplification of the method is described which enables the practitioner to make the determination of blood indican in his own office with adequate accuracy and with a minimum of time and effort.

TABLE 8.—*Intermediate Indicanemia; Uncertain Prognosis*

			Blood Chemistry						
No.; Patient	Race, Sex and Age	Clinical Diagnosis	Date, 1929	Urea Nitrogen, Mg. per 100 Cc. of Blood	Creatinine	Indican +	Result	(1929)	Postmortem Data
98 E. N.	White Male 43	Chronic diffuse nephritis	4/ 6 4/18 5/ 6 5/22	51.3 48.0 42.0 51.0	3.3 3.3 2.6 2.6	2 3 4 4	Death in uremia	5/27	(P.M. 445) Subacute glomerulonephritis (intracapillary)
99 L. N.	White Male 28	Subchronic diffuse nephritis	2/24 2/27 3/ 5 3/16 4/ 5	60.0 100.0 27.5 19.0 44.0	4.6 6.3 2.0 1.7 2.8	1 2 1 2 0	Discharged, recovered	4/ 8	
100 T. W.	White Male 33	Chronic diffuse nephritis	2/22 3/22	80.0 70.0	10.0 8.5	2 4	Death in uremia	4/ 1	
101 A. P.	Colored Male 56	Chronic diffuse nephritis	3/21 4/ 7	62.0 43.0	4.4 3.0	2 1	Discharged, recovered	4/ 9	
102 J. T.	White Male 54	Pyelonephritis	3/16	51.0	3.0	2	Died of bronchopneumonia	3/19	
103 C. R.	White Male 77	Hypertensive disease of the heart	2/23 2/28	21.0 24.0	2.0 1.7	2 1	Died of cardiac decompensation	3/30	
104 J. W.	White Female 39	Hypertensive disease of the heart	4/17	39.0	2.5	2	Died of cardiac decompensation	4/19	

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CAROTINEMIA AND DIABETES

II. THE RELATIONSHIP BETWEEN THE SUGAR, CHOLESTEROL AND CAROTIN CONTENTS OF BLOOD PLASMA *

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In a previous communication,[1] I reported the results of an investigation on the phenomenon of xanthosis occurring during the course of diabetes mellitus. The incidence of this condition does not appear to be great. It was found in only fifty-nine of 1,400 diabetic patients, selected at random at the clinic for patients with diabetes in the Montreal General Hospital. The significance of xanthosis was discussed. It was suggested that a diet high in vegetable content to which the diabetic patient is subjected and to which this condition is generally attributed is not the only factor involved. Evidence favoring this view was that thirteen of the fifty-nine patients with this skin condition had never been on special diets prior to its detection, and that, so far as I am aware, it is not found in vegetarians. That it may be of prognostic importance was suggested by the fact that in the group of diabetic patients with this condition the incidence of those requiring insulin was high. Forty-four of the fifty-nine patients with diabetes, that is, an incidence of 74.5 per cent, required this drug; whereas, only 18 per cent of all of the patients in the clinic were using it. The incidence of arteriosclerosis was also high. Thirty-six of the fifty-nine patients, that is, an incidence of 61 per cent, had some evidence of it; whereas, it was present in only 22 per cent of all cases. Apropos of these patients with arteriosclerosis, it may here be mentioned that the average duration of diabetes in these cases was only 3.1 years. Compared with the whole group of diabetic patients, this is a rather short period for one to acquire this complication. Hypercholesterolemia was also a marked feature, but there were difficulties in interpreting this phenomenon. Other features of note were that insulin edema was found in four cases, hyperglycemia difficult to control with insulin in eleven cases, and raised renal threshold for sugar in six cases. In view of these observations, it was suggested that xanthosis occurring during the course of diabetes mellitus indicated an unfavorable prognosis, and its study deserves more consideration than it has been given hitherto.

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In order to test the correctness of this conclusion it was considered advisable to make a more complete clinical and laboratory study of this phenomenon. Difficulty was at once encountered. When there is well marked xanthosis, that is, when there is the characteristic yellow discoloration of the nasolabial folds, the palms and the soles, its detection is not difficult. Various grades of discoloration are met with, however, and when slight, these may easily be confused with the color of the skin associated with the various anemias and with icterus. It is obvious that the former condition may be ruled out by estimations of the hemoglobin and the latter by estimations of the bilirubin content of the blood by means of the van den Bergh reaction.

In spite of the aforementioned precautions, doubtful cases of xanthosis may be met with. In order to make certain of the presence or absence of this condition, it is necessary to estimate directly the lipochrome content of the blood. For this purpose, estimation of the carotin content only appears to suffice. This is based on the observations of van den Bergh and Snapper,[2] Bürger and Reinhart,[3] Salomon,[4] Hess and Myers,[5] Head and Johnson,[6] Stoner [7] and Connor.[8] Chemical and spectroscopic tests support the view that xanthosis is due chiefly to excess quantities of carotin.

Through the efforts of Tswett [9] and Willstaetter and Mieg,[10] and, later, of Palmer and others [11] who made an extensive study of the pigments of biologic materials (milk, butter, eggs, agricultural products), methods for such a study are now available. Carotin can now readily be detected and estimated quantitatively. This depends on three properties of this pigment, namely, its solubilities in alcohol and petroleum-ether, its failure to be adsorbed onto calcium carbonate and its spectroscopic bands.

For routine purposes, excess quantities of carotin in the blood may readily be detected by a method based on the following solubility properties of this and other pigments met with clinically. Hess and Myers, Connor, and also Stoner, employed this principle. The latter, however, did not record the origin of his method.

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2. Van den Bergh and Snapper: Deutsches Arch. f. klin. Med. **110**:540, 1913.
3. Bürger and Reinhart: Deutsche med. Wchnschr. **45**:430, 1919.
4. Salomon: München. med. Wchnschr. **66**:564, 1919.
5. Hess, A. F., and Myers, V. C.: Carotinemia: A New Clinical Picture, J. A. M. A. **73**:1743 (Dec. 6) 1919.
6. Head, G. D., and Johnson, R. A.: Carotinemia, Arch. Int. Med. **28**:268 (Sept.) 1921.
7. Stoner: Am. J. M. Sc. **175**:419, 1919.
8. Connor: Am. J. Path. **14**:227, 235, 293, 1928.
9. Tswett: Ber. d. bot. Gesell. **24**:316, 384, 1906; **29**:630, 1911.
10. Willstaetter and Mieg: Ann. d. Chem. **355**:1, 1907.
11. Palmer, J. Biol. Chem. **17**:191, 1904.

Palmer and his co-workers stated: "It has been found that carotin cannot be extracted from its solution in low-boiling-point petroleum-ether by 80 to 90 per cent alcohol, while low-boiling-point petroleum-ether will quantitatively extract carotin from its solution in 80 to 90 per cent alcohol."

The observation that carotin can be removed from its solution in alcohol by petroleum-ether has an important bearing on the method used in this study. Much of the carotin in the blood may be bound to the proteins, either chemically or physically (adsorption). In either case, the pigment is readily set free from the proteins by precipitating the latter with 95 per cent alcohol. Of importance also are other blood pigments frequently met with clinically, particularly bile. Some of these are also soluble in alcohol. They remain in the alcohol, however, when the latter is mixed with low boiling point petroleum-ether and the mixture is shaken. For example, even with blood from patients with marked jaundice, showing intense reactions with the van den Bergh test, none of the pigments responsible for this color reaction are removed from the alcoholic fraction of the mixture by the petroleum-ether. Under the same conditions, low boiling point petroleum-ether also fails to remove pigments liberated from hemolyzed blood corpuscles. The following tests readily demonstrate the foregoing phenomena.

To 3 cc. of plasma, containing large quantities of bilirubin or hemolyzed blood, an amount of plaster of paris is added sufficient to bring the mixture to the consistency of a paste. To this is added 3 cc. of 95 per cent ethyl alcohol. The mixture is shaken for a few minutes. When precipitation of the proteins is complete, 3 cc. of petroleum-ether (boiling point from 30-50 C.) is added. The mixture is shaken for ten minutes and then centrifuged. It will be found that all of the bilirubin or hemolyzed blood pigments remain in the alcoholic fraction.

Even in normal subjects, the layer of ether may acquire a yellowish tinge. This, or the greater part of it, is vegetable pigment (carotin). (Practically all normal blood contains minute traces of vegetable pigment. This will be referred to presently.)

If this test is applied to plasma containing large amounts of carotin, all of the latter will be found in the upper, that is, in the ether layer. The solution of carotin in ether may now be removed and placed in a clean dry test tube for purposes of comparison with standards.

For quantitative work in this laboratory a solution of oleic acid in petroleum ether [12] is used, and the results are expressed in terms of units. By the foregoing method, the maximum amount of pigment found in the

12. This solution does not keep well. It is renewed weekly. For a permanent standard, potassium bichromate may be used, as recommended by Connor (J. Biol. Chem. **77**:619, 1928).

blood of more than 100 normal subjects gave a color corresponding to that of a 10 per cent solution (by volume) of oleic acid. This is regarded as one unit of pigment.

This report concerns the results of an investigation of the bloods of 500 patients with diabetes selected at random. In each case the following analyses were made on the same sample: (*1*) sugar; (*2*) cholesterol; (*3*) bilirubin (van den Bergh test) and (*4*) carotin.

An attempt was first made to determine the different degrees of carotinemia and their incidences. The results are shown in table 1. It

TABLE 1.—*Degrees of Carotinemia Found Among Five Hundred Diabetic Patients and Their Incidences*

Carotin (Units)	Incidence
1	74
2	98
3	98
4	74
5	59
6	65
7	16
8	9
9	3
10	2
11	2

TABLE 2.—*Absence of Relationship Between Sugar and Carotin Content of Blood*

Carotin (Units)	Blood Sugar (per Cent)		
	High	Low	Average
1	0.416	0.084	0.174
2	0.555	0.090	0.202
3	0.295	0.091	0.167
4	0.454	0.063	0.167
5	0.434	0.091	0.174
6	0.588	0.074	0.178
7	0.454	0.116	0.226
8	0.285	0.103	0.192
9*	0.250	0.149	
10*	0.143	0.109	
11*	0.400	0.204	

* The incidences of these concentrations of carotin were too low to attach significance to the data.

will be observed, as pointed out in my first report,[1] that most diabetic patients have more pigment than do normal subjects. Only seventy-four, that is, about 15 per cent of the total number of patients observed had quantities within the normal limits. The great majority had between 1 and 5 units. This amount is apparently insufficient to produce obvious xanthosis. All of the fifty-nine patients with xanthosis, detected clinically and without laboratory aid, had 6 units or more of this pigment.

An attempt was then made to determine whether there was a relationship between sugar and carotin contents of blood. No relationship was found. This is shown in table 2. These results are those one would, *a priori*, expect if there is a relationship between prognosis and

carotinemia, since, as is generally known, prognosis and sugar content of blood are not related. An analogy may be found in cholesterol studies. Prognosis and plasma cholesterols are related;[13] yet there is no relationship between the latter and blood sugar. This is shown in table 3.

These results led to an investigation, the importance of which is obvious from the following: If both plasma cholesterol and carotin are related to prognosis, one would expect to find some relationship between carotin and cholesterol. Such a relationship was found.

In the interpretation of these observations there are two important considerations. A large number of diabetic patients have disease of the biliary passages. This has been shown in Joslin's clinic as well as in the one at the Montreal General Hospital.[14] In cases of disease of the biliary passages the cholesterol content of the blood may be increased. As a matter of fact, the blood of eleven of fifty-nine patients with

TABLE 3.—*Absence of Relationship Between Sugar and Cholesterol Contents of Blood in Five Hundred Cases of Diabetes Mellitus*

Blood Sugar, per Cent	Number of Cases	Average Cholesterol, per Cent
0.120	120	0.312
0.121-0.200	228	0.290
0.201-0.250	65	0.286
0.251-0.300	37	0.290
0.301-0.350	21	0.292
0.351-0.400	11	0.354
0.401-0.450	3	0.241
0.451-0.500	4	0.342
0.500	3	0.261

xanthosis gave positive van den Bergh reactions. This test, when positive, as is well known, is a reliable indication of biliary disease in the absence of hemolytic processes. Such cases should, obviously, be excluded from this study. This, it may be noted, was done in the first investigation.[1] The results, however, did not affect the average. In fact, the highest cholesterol value was found in the absence of a positive van den Bergh reaction, namely, 0.56 per cent.

The data showing relationship between cholesterol and carotin contents of blood are briefly summarized in table 4. Here are recorded the high, low and average cholesterol values corresponding to the different degrees of carotinemia. It will be observed that as the degree

13. Joslin, E. D.; Bloor, W. R., and Gray, H.: The Blood Lipoids in Diabetes, **69**:375 (Aug. 4) 1917. Gray, H.: Am. J. M. Sc. **168**:35, 1924. Rabinowitch, I. M.: Canad. M. A. J. **17**:171, 1927; The Cholesterol Content of Blood Plasma in Diabetes Mellitus, Arch. Int. Med. **43**:363 (March) 1929.

14. Jones, C. M., and Others: Pancreatic and Hepatic Activity in Diabetes Mellitus, Arch. Int. Med. **35**:315 (March) 1925. Rabinowitch, I. M.: Brit. J. Exper. Path. **7**:155, 1926.

of carotinemia increases, the average cholesterol also increases, but not to the same extent.

In order to determine whether the differences noted between the different groups were significant, the data were treated statistically. For this purpose the following values were calculated for each of the aforementioned groups: (*a*) number of cases; (*b*) average cholesterol (mean) (*c*) standard deviation; and (*d*) probable error of the mean.

With this information it is possible to determine whether the difference obtained between the means of any two groups one wishes to compare are significant or merely the result of chance. Comparisons were made between the following groups: 1 and 2; 2 and 3; 3 and 4;

TABLE 4.—*Statistical Demonstration of the Relationship Found Between the Cholesterol and Carotin Contents of Blood in Five Hundred Cases of Diabetes Mellitus*

Units Carotin	Number of Patients	Plasma Cholesterol, per Cent			Standard Deviation	Probable Error of Mean	Probable Error of Difference Between Means	Difference	Difference / Probable Error of Difference
		High	Low	Arithmetical Mean					
1	74	0.354	0.109	0.209	62.6	4.91			
							5.8	34	5.8
2	98	0.666	0.073	0.243	45.6	3.10			
							6.4	27	4.2
3	98	0.883	0.181	0.270	82.1	5.59			
							9.7	34	3.5
4	74	0.800	0.133	0.304	102.8	8.05			
							11.0	5	0.45
5	59	0.483	0.147	0.309	85.9	7.50			
							14.7	55	3.7
6	65	0.794	0.177	0.364	151.7	12.60			
							53.3	105	1.9
7	16	0.793	0.191	0.469	307.7	51.84			
							69.0	18	0.26
8	9	0.980	0.297	0.487	208.4	46.80			

4 and 5; 5 and 6; 6 and 7, and 7 and 8. The number of observations in the remaining group were too small to allow for conclusions.

The necessary further calculations were as follows: (*a*) the difference between the means of the groups to be compared; (*b*) the probable error of the difference, and (*c*) the ratio of the difference to the probable error of the difference.

The results of these calculations are shown in table 4.

It will be seen (last column) that with the exception of the differences noted between groups 4 and 5, and groups 7 and 8, there is statistical proof that the differences noted between the means of the different groups compared were not accidental. In other words, carotin and cholesterol are related.

It may here be observed that the lowest ratios obtained included the groups which had the least number of subjects. In view of the small number of observations, limited significance could be attached to these ratios in any event.

These results led to certain observations. Since plants contain substances (sterols) allied chemically to cholesterol, is it not possible that herein lies the explanation of the correlation found? That this is not the only explanation, however, is suggested by the fact that some subjects had enormous quantities of carotin and at the same time had normal cholesterol values, and, conversely, a number of persons had excessive quantities of cholesterol and practically normal amounts of carotin. Thus (table 4):

Cholesterol (%)	Carotin (units)
0.666	2
0.191	7

Numerous similar examples were met with in this series.

SUMMARY

It would appear that for some unknown reason certain diabetic patients retain ingested vegetable pigments to a greater extent than others. The importance of this observation is that such persons usually do not appear to do well clinically, and the majority have a high cholesterol content of the blood. Though large amounts of carotin may be responsible for high values of plasma cholesterol because of their chemical relationship, this does not appear to be the only cause. Since there is a relationship between cholesterol and carotin and in view of the unfavorable prognosis for patients with high cholesterols, it is suggested that marked carotinemia also suggests an unfavorable prognosis.

As with cholesterols, there are exceptional cases. In such instances it was found that carotin may accumulate in the blood rapidly and yet no other evidence of downward progress may be noted. Both of these phenomena require further study. These exceptions do not alter the value of studies of the cholesterol content in the majority of cases; neither should they, therefore, do so in the cases of carotin.

Since cholesterol and carotin contents of blood do not always parallel each other, it is reasonable to assume that there are two different factors involved, though in a great majority of cases both of them probably operate. To elucidate the picture further, time and careful clinical studies are necessary. The purpose of the foregoing report is to demonstrate the probability that carotinemia has a greater clinical significance in diabetes mellitus than that generally attached to it, and to prompt further study of this phenomenon by others, particularly those interested in diabetes. The treatment of patients with diabetes, much more satisfactory as it may be today compared with the past, is far from ideal. The degree of approach can be only in direct proportion to the knowledge concerning the different phases of the disease.

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ORTHOPNEA

ITS RELATION TO THE INCREASED VENOUS PRESSURE OF MYOCARDIAL FAILURE *

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The factors that impel patients with myocardial failure of the congestive type to sit up in bed in order to breathe more comfortably have aroused the curiosity of many investigators. Numerous theories of the pathogenesis of orthopnea have been advanced, but none completely accounts for all the characteristics of the phenomenon.

REVIEW OF THE LITERATURE

The earlier writers generally believed that the sitting posture was assumed because the accessory muscles of inspiration could then be used to greater advantage. Hofbauer,[1] however, showed that the chief respiratory difficulty in orthopneic patients was expiratory rather than inspiratory, and that the accessory muscles of expiration did not function more efficiently in the upright posture. According to him,[2] the orthopneic position provides relief because it secures the following mechanical advantages: 1. The lower position of the diaphragm and the consequent increased capacity of the thorax increases the elastic tension of the lungs and so facilitates expiration. The observation of Aron [3] that the negative intrathoracic pressure is greater in the sitting than in the recumbent posture supports this hypothesis. 2. The increased negative intrathoracic pressure in the upright position also aids the right ventricle in maintaining blood flow through the lungs. 3. In the recumbent position, the abdominal viscera, by falling against the vertebral column and the posterior half of the diaphragm, not only

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* From the Thorndike Memorial Laboratory, Boston City Hospital, the Medical Research Laboratories, Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

* Read in abstract before the American Society for Clinical Investigation, Atlantic City, N. J., May 6, 1929.

1. Hofbauer, L.: Ursachen der Orthopnoe, Ztschr. f. klin. Med. **61**:389, 1907.

2. Hofbauer, L.: Ursachen der Orthopnoe: II. Die kardiale Orthopnoe, Ztschr. f. klin. Med. **79**:128, 1914.

3. Aron, E.: Ueber einen Versuch den intrapleuralen Druck am lebenden Menschen zu messen, Virchows Arch. f. path. Anat. **126**:517, 1891.

interfere with diaphragmatic movements but also diminish the aperture of the quadrilateral foramen and so obstruct the return of blood in the inferior vena cava. 4. The abdominal muscles exert an efficacious pumping action on the viscera and inferior vena cava only in the upright position. Hofbauer [2] asserted that cardiac orthopnea could be explained completely on this purely mechanical basis.

Bohr [4] found a decrease in the vital capacity, reserve air, and middle capacity of the lungs and an increase in the complemental air in the recumbent as compared with the sitting posture. Rubow [5] demonstrated that in patients with myocardial failure there is a relative increase in the middle capacity and believed that the orthopneic position is assumed in order to obtain the greatest possible total and middle capacity of the lungs. He believed that any increase in the middle capacity diminishes the resistance to blood flow in the pulmonary capillaries by reducing the tortuosity of these vessels.

Christie and Beams [6] recently reported that the average vital capacity of the lungs of 290 normal people while lying was 5.5 per cent less than while sitting. Nine patients with orthopnea of necessity with an average reduction of 69.5 per cent from the estimated normal vital capacity of the lungs lost an additional 26.7 per cent on lying down.[7] Fourteen patients with orthopnea of choice with an average reduction of 55 per cent lost an additional 12.5 per cent on lying down. Nineteen patients with dimished vital capacities, but without orthopnea, had an average reduction of 36 per cent of the estimated normal and lost only an additional 4.7 per cent on lying down. Christie and Beams [7] believed that the increased vital capacity of the lungs in the upright position is the primary factor in the production of orthopnea.

Haldane, Meakins and Priestley [8] showed that even in healthy persons the recumbent position accentuates the unevenness with which the lungs normally expand and so tends to produce anoxemia. This tendency in normal persons is partly counteracted by deeper inspiration, a compensatory mechanism not available to patients suffering from

4. Bohr, C.: Die funktionellen Aenderungen in der Mittellage und Vitalkapazität der Lungen, Deutsche Arch. f. klin. Med. **88**:385, 1907.

5. Rubow, V.: Die kardiale Dyspnoe, Ergebn. d. inn. Med. u. Kinderh. **3**:71, 1909.

6. Christie, C. D., and Beams, A. J.: The Estimation of Normal Vital Capacity, with Especial Reference to the Effect of Posture, Arch. Int. Med. **30**:34 (July) 1922.

7. Christie, C. D., and Beams, A. J.: Orthopnea, Arch. Int. Med. **31**:85 (Jan.) 1923.

8. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: The Effects of Shallow Breathing, J. Physiol. **52**:433, 1919.

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congestive failure. Consequently, in congestive failure, the mixed arterial blood leaving the lungs is less well oxygenated in the recumbent than in the sitting position, and the respiratory center therefore is exposed to increased anoxemia. If the patient sits up, however, the lungs expand more evenly, the anoxemia is diminished, and the partial asphyxia of the respiratory center is lessened. Haldane, Meakins and Priestley believed that their observations explain the occurrence of orthopnea in myocardial failure.

Recently, Wilson,[9] apparently unacquainted with the work of Bohr,[4] reinvestigated the effect of posture on the volume of the reserve air of the lungs in normal persons and found a marked reduction in the recumbent as compared with the erect position. He believed this decreased volume of the reserve air in the recumbent position led to a diminution in the oxygen content of the mixed arterial blood leaving the lungs. His explanation for orthopnea is therefore closely related to that of Haldane, Meakins and Priestley.[8]

Sahli [10] stated that the accessory muscles of respiration can be used to advantage only in the upright posture, and that this position may relieve the diaphragm from the pressure due to fluid within the abdomen. He also stated that the venous congestion of the brain and particularly of the respiratory center was possibly relieved in the sitting position by the action of gravity, and that the accumulation of blood in the lower extremities in this position diminished pulmonary congestion and decreased the work of the heart. He offered no data in support of these hypotheses. Hill [11] also believed pulmonary congestion to be diminished in the orthopneic position because of drainage by gravity of a large quantity of blood into the splanchnic area.

Field and Bock,[12] in 1925, found that the average minute volume output of the heart in the sitting position was 76 per cent, and in the upright position only 50 per cent, of that in the recumbent posture. They believed that an accumulation of blood in the legs and splanchnic area occurs in the sitting and standing positions, and that the resultant diminished venous return to the heart leads to decreased cardiac output and lessened pulmonary congestion. Similar observations on the minute volume output of the heart have been reported by several other

9. Wilson, W. H.: The Influence of Posture on the Volume of the Reserve Air, J. Physiol. **64**:54, 1928.

10. Sahli, H.: Lehrbuch der klinischen Untersuchungsmethoden, ed. 1, Leipzig, Franz Deuticke, 1894.

11. Hill, L.: The Influence of the Force of Gravity on the Circulation. J. Physiol. **18**:15, 1895.

12. Field, H., Jr., and Bock, A. V.: Orthopnoea and the Effect of Posture upon the Rate of Blood Flow, J. Clin. Investigation **2**:67, 1925.

investigators[13] using the same method or the ethyl iodide method of Henderson and Haggard.[14] Grollman,[15] however, using the nitrous oxide method of Marshall and Grollman,[16] found a practically constant circulatory minute volume in the recumbent, sitting and standing positions and attributed the differences observed by previous workers to errors inherent in the methods employed.

A NEW HYPOTHESIS OF ORTHOPNEA

We believe that the orthopneic position benefits the patient with congestive circulatory failure because it secures a maximum blood flow about the respiratory center and thereby relieves the patient from the distress due to partial asphyxia in that area. The mechanism of this is conceived to be as follows. Physiologic investigations[17] indicate that the blood flow in the capillaries is dependent on the pressure gradient in these vessels. The greater the difference in pressure along the capillary, the greater the blood flow. An elevation of the venous pressure, therefore, diminishes capillary blood flow in the absence of any striking increase in arteriolar blood pressure. Other factors remaining equal, increased venous pressure leads to stagnation of blood in the capillaries and so produces stagnation anoxemia. It is well known[18] that in myocardial failure the peripheral venous pressure is increased roughly in proportion to the degree of decompensation.

The orthopneic position, in our opinion, relieves the respiratory center of the increased pressure within the veins of that area in the following manner. There are no efficient valves in the veins between the cerebral capillaries and the right auricle.[19] If a patient with uncomplicated cardiovascular failure and a venous pressure at the right auricle equivalent to 15 cm. of water lies flat in bed, there is a corresponding

13. Henderson, Y., and Haggard, H. W.: The Circulation and Its Measurement, Am. J. Physiol. **73**:193, 1925. Lawrence, J. S.; Hurxthal, L. M., and Bock, A. V.: Variations in Flow with Changes in Position in Normal and Pathologic Subjects, J. Clin. Investigation **3**:613, 1927. Rosen, I. T., and White, H. L.: The Relation of Pulse Pressure to Stroke Volume, Am. J. Physiol. **78**: 168, 1926. Turner, A. H.: Circulatory Minute Volumes of Healthy Young Women in Reclining, Sitting and Standing Positions, Am. J. Physiol. **80**:601, 1927.

14. Henderson and Haggard (footnote 13, first reference).

15. Grollman, A.: The Effect of Variations in Posture on the Output of the Human Heart, Am. J. Physiol. **86**:285, 1928.

16. Marshall, E. K., and Grollman, A.: A Method for the Determination of the Circulatory Minute Volume in Man, Am. J. Physiol. **86**:117, 1928.

17. Bayliss, W. M., and Starling, E. H.: Observations on Venous Pressures and Their Relationship to Capillary Pressures, J. Physiol. **16**:159, 1894.

18. Eyster, J. A. E., and Middleton, W. S.: Clinical Studies on Venous Pressure, Arch. Int. Med. **34**:228 (Aug.) 1924.

19. Hill, L.: Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896.

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pressure of 15 cm. of water in the veins about the respiratory center (fig. 1). This results in diminished blood flow in the capillaries and stagnation anoxemia in this region. If, however, the patient sits up, so that the respiratory center is 15 cm. above the right auricle, the pressure in the veins about the center is zero (fig. 2). The blood flow in the capillaries leading to these veins would then be increased, the respiratory center would receive a more adequate supply of blood, and the subjective respiratory distress would be relieved.

METHOD

To test the validity of this hypothesis, the following studies were undertaken:

Relation between Height of Venous Pressure and Degree of Orthopnea.—If the foregoing hypothesis is valid, one might expect that the degree of orthopnea would closely parallel the degree to which the venous pressure is increased. It is, of course, impossible to measure the venous pressure of the vessels about the respiratory center, but

Fig. 1.—The relation between the pressure in the right auricle and in the veins about the respiratory center, in the recumbent position. In the recumbent position, the right auricle and the respiratory center are in approximately the same horizontal plane. The pressure in the veins about the respiratory center, therefore, is the same as that in the right auricle.

Weed and Hughson [20] have shown that, in cats and dogs, brachial and cerebral venous pressures are identical in the recumbent position. In the present investigation, the relation between the height of the systemic venous pressure and the degree of orthopnea was studied in a series of patients with uncomplicated myocardial failure. The venous pressure was measured by the direct venipuncture method of Moritz and Tabora,[21] using the median basilic or median cephalic vein. The pressure was measured in the recumbent position, unless the patient was unable to endure the discomfort. A minority of the measurements were taken,

20. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol. **108**:101, 1921.

21. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsche Arch. f. klin. Med. **98**:475, 1910.

therefore, with the patient somewhat elevated. All observations were made with the arm resting at the level of the right auricle. The first measurements were made as soon as possible after the patients were admitted to the hospital, and subsequent observations were carried out at intervals of from three to five days. Successive measurements of venous pressure on each patient were taken at the same time of day, usually between 2 and 4 o'clock in the afternoon, in order to avoid

Fig. 2.—The relation between the pressure in the right auricle and in the veins about the respiratory center, in the sitting position. When the patient assumes a sufficiently elevated position, the respiratory center is above the level of the meniscus of the column of venous blood extending upward from the right auricle. The pressure in the veins about the respiratory center, therefore, becomes zero.

the error incident to diurnal fluctuation of the pressure.[22] Other precautions outlined by previous investigators,[23] were observed in making

22. Hooker, D. R.: Observations on the Venous Blood Pressure in Man, Am. J. Physiol. **35**:73, 1914.

23. Eyster, J. A. E.: Venous Pressure and Its Clinical Applications, Physiol. Rev. **6**:281, 1926. Runge, H.: Ueber den Venandrucke im Schwangerschaft. Geburt und Wochenbett, Arch. f. Gynäk. **22**:142, 1924.

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the measurements of the venous pressure. The degree of orthopnea was ascertained by measuring the perpendicular distance between the level of the right auricle and a point corresponding to the respiratory center, namely the external occipital protuberance. These measurements were made in the evening after the wards had been darkened, and the patients had had an opportunity to assume the most comfortable position for the night. Sedatives were withheld until these observations were finished, in order not to influence the sensitivity of the respiratory center. In estimating the venous pressure and the degree of orthopnea, the position of the right auricle was ascertained in the following manner: With the patient in the recumbent posture, the right auricle is 5 cm. below the fourth chondrosternal junction,[21] while with the patient sitting at an elevation of 90 degrees, both are at the same level. At all intermediate positions of the patient, the difference between the level of the right auricle and the fourth chondrosternal junction would range between zero and 5 cm. Thus, at an elevation of 45 degrees, the auricle was assumed to be 2.5 cm. below the plane of the fourth chondrosternal junction. The points taken to represent the level of the right auricle and the respiratory center were not, of course, anatomically precise, but nevertheless, were satisfactory for purposes of comparison. The same points were used in the successive observations on the same person, so that any absolute errors would tend to cancel out.

Flexion of the Head.—Previous theories of orthopnea have stressed the significance of changes within the chest or abdomen, whereas the present theory places more emphasis on the importance of the elevation of the head. It therefore seemed that the relative importance of these different factors could be differentiated by elevating the head without elevating the abdomen or thorax. Accordingly, all orthopedic patients were placed in the recumbent position, and as soon as they became acutely distressed the head was flexed forward, care being taken not to alter the position of the thorax. The degree of respiratory distress was observed, and the patient was encouraged to describe any differences in his subjective sensations.

Vital Capacity of the Lungs.—Because previous investigators had stressed the importance of the vital capacity of the lungs in the pathogenesis of orthopnea, the vital capacity was recorded in the orthopneic position at the time of each observation, and whenever feasible, in the recumbent position, both with the head flat and with the head flexed on the chest. The theoretical normal vital capacity of each patient was estimated according to his surface area,[24] and from this the percentage

24. West, H. F.: Clinical Studies on the Respiration: VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

reduction observed in the sitting position was calculated. For example, a man whose surface area is 1.7 square meters has an estimated normal vital capacity of 4,250 cc. If the actually observed vital capacity is 2,000 cc., there is a reduction from the estimated normal of 52.9 per cent.

RESULTS

Relation between Height of Venous Pressure and the Degree of Orthopnea.—Eighty-two measurements of the venous pressure and the perpendicular distance between the occipital protuberance and the level of the right auricle were made in twenty-two patients. A

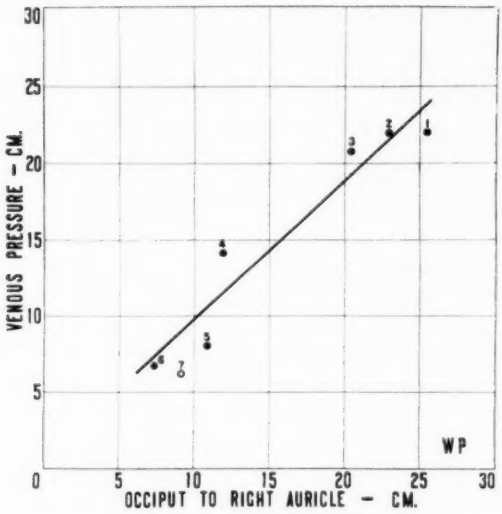

Fig. 3.—Comparisons of the height of venous pressure and the degree of orthopnea in patient W. P. Sequence of measurements is indicated by the numbers above the dots. The open dot (no. 7) indicates the absence of orthopnea of necessity, although orthopnea of choice still was present.

parallelism between the height of venous pressure and the degree of orthopnea was observed. In general, the higher the venous pressure, the greater the orthopnea. Figure 3 shows the results obtained in a typical case. On admission to the hospital, this patient had advanced myocardial failure; the venous pressure was 22 cm. and the degree of orthopnea 25.5 cm. Subsequent observations were made at four day intervals, and the consecutive measurements are represented by the numbered dots in the figure. During the first eight days the venous pressure and the degree of orthopnea diminished only slightly; but with clinical improvement following venesection of 500 cc. of blood.

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both decreased rapidly and approximately to the same degree. At the time of the seventh measurement, the venous pressure was 6.1 cm., and orthopnea of necessity had disappeared. The patient no longer experienced respiratory distress in the recumbent position, but still assumed a slightly elevated posture when left to himself. Figure 4 presents the eighty-two comparisons of venous pressure and degree of orthopnea in all patients studied. The degree of orthopnea varied from 4.7 to 25.5 cm. The venous pressure readings falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses in the figure. There is a considerable spread of

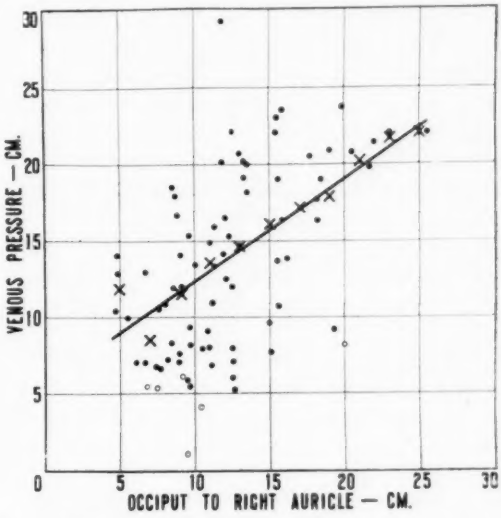

Fig. 4.—Comparisons of the height of venous pressure and the degree of orthopnea. A composite chart. Open dots represent measurements taken after orthopnea of necessity had disappeared although orthopnea of choice still was present. The venous pressure readings falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses.

the individual measurements, but the close parallelism between average venous pressure and degree of orthopnea strongly supports the hypothesis.

Flexion of Head on the Thorax in the Recumbent Position.—Simple elevation of the head by flexion of it on the thorax when the patient was flat in bed produced a conspicuous diminution of respiratory distress in all but one instance. As might be expected, this relief usually was only partial. The one exception was a patient with a venous pressure of 23 cm., who obtained only slight relief in the 90 degree sitting

position and was much more comfortable when leaning forward and supporting himself with his hands. Because of weakness, he was unable to maintain the latter position for long periods and usually remained at an elevation of about 60 degrees. It is of interest that in the more comfortable position of sitting forward, the distance from the external occipital protuberance to the right auricle was 32.5 cm., whereas in the less comfortable upright position of 60 degrees the distance was 19.5 cm.

Vital Capacity of the Lungs.—In order to be certain that the relief experienced by the subjects on flexion of the head was not due to an increase in the vital capacity of the lungs, measurement of the latter was made with the head level with the rest of the body and with the head flexed. In one fourth of the observations (table) the vital capacity was unchanged, while in the others it was either diminished by as much as 200 cc. or increased by as much as 250 cc. Since the subjects experienced relief regardless of a diminution or an increase in the vital capacity, this factor must be considered of small importance. For the entire group, the vital capacity in the position with the head flexed showed an average increase of 14 cc.

Since other observers have attributed the increased comfort obtained in the sitting position to an increase in the vital capacity of the lungs, the latter was measured, whenever possible, in both the recumbent and the upright position. Sixty-three comparisons of the vital capacity in the two positions were made in eighteen subjects. The results obtained (table) do not corroborate the observation of Christie and Beams [7] that there is an important further reduction of the already greatly diminished vital capacity of the lungs in patients with orthopnea of necessity when they assume the recumbent position. Christie and Beams, in nine observations on nine patients with orthopnea of necessity, observed that the vital capacity averaged 26.7 per cent less on lying down. In sixty-three measurements on eighteen similar patients, we found the vital capacity averaged only 8.3 per cent less in the recumbent position. The decrease ranged from zero to 23.9 per cent of the vital capacity in the sitting position, but was less than 5 per cent in twenty-two of the sixty-three observations. In seven observations there was no change, while in only three did the decrease amount to 20 per cent or more. In these sixty-three measurements, the average vital capacity in the orthopneic position was 41.6 per cent of the estimated normal. These results are not strictly comparable with those of Christie and Beams since, in the present series, the vital capacities in the sitting posture were measured at the elevation which the patients regarded as most comfortable, while Christie and Beams apparently recorded the values for the 90 degree position. Our studies demon-

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strate that orthopnea of necessity does occur in patients who do not show a great reduction of the vital capacity of the lungs on changing from the sitting to the recumbent posture.

To gain further knowledge of the importance of the vital capacity of the lungs in the mechanism of orthopnea, the percentage reduction of the vital capacity in the sitting position was compared with the perpendicular distance between the occipital protuberance and the level of the right auricle (figure 5). In striking contrast to the definite correlation between the venous pressure and the degree of orthopnea, no close relationship was apparent between the reduction in the vital capacity of the lungs and the degree of orthopnea. While both orthopnea

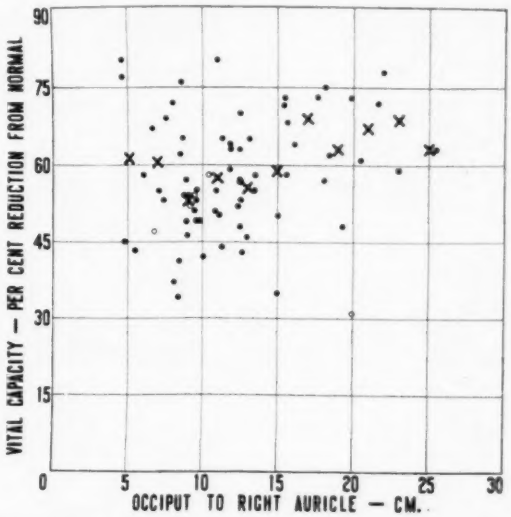

Fig. 5.—Comparisons of the percentage reduction of the vital capacity of the lungs and the degree of orthopnea. A composite chart. Open dots represent measurements taken after orthopnea of necessity had disappeared, although orthopnea of choice still was present. The percentages of reduction of the vital capacity falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses.

of necessity and a greatly reduced vital capacity occur in advanced congestive failure, no parallelism between the two is evident. Hence, the extent of the diminution of the vital capacity does not appear to play an important rôle in determining the degree of elevation which gives the patient maximum relief. Thus in the case of W. P. (table), the vital capacity during the first twelve days remained practically unchanged. During this time the orthopnea of necessity diminished one half, and the venous pressure decreased from 22 to 14.1 cm.

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Summary of Observations on Venous Pressure, Vital Capacity of the Lungs, and Degree of Orthopnea

Subject	Age	Diagnosis	Date	Venous Pressure, Cm. of Water	Occipitial Protuberance to Right Auricle, Cm.	Vital Capacity					Comment
						Estimated Normal, Cc.	In Orthopneic Position, Cc.	Reduction from Estimated Normal, per Cent	In Recumbent Position with Head Flat, Cc.	Decrease from Orthopneic Position, per Cent	Change on Elevating Head, Cc.	
W. P.	54	Arteriosclerotic heart disease, auricular fibrillation	8/ 2/27	22.0	25.5	4,450	1,650	63	1,500	9.1	+50	
			8/ 6/27	22.0	23.0	.....	1,800	59	1,650	8.3	0	
			8/10/27	20.7	20.5	.....	1,750	61	1,625	7.1	+25	Venesection, 500 cc. on 8/13/27
			8/14/27	14.1	11.9	.....	1,650	63	1,450	12.1	0	
			8/18/27	8.0	10.9	.....	2,000	55	1,925	3.8	0	
			8/22/27	6.7	7.4	.....	2,100	53	1,900	9.5	0	
			8/26/27	6.1	9.2	.....	2,150	52	1,975	8.1	−75	No orthopnea of necessity
P. G.	66	Arteriosclerotic heart disease, auricular fibrillation	8/11/27	19.1	13.3	.....	.....	..	.....	....	....	Patient uncooperative; no studies of vital capacity
			8/15/27	7.0	6.7							
			8/20/27	6.6	7.7							
			8/25/27	5.3	7.5	.....	.....	..	.....	....	....	No orthopnea of necessity
S. K.	14	Rheumatic heart disease, mitral stenosis, auricular fibrillation	8/11/27	13.7	15.5	.....	.....	..	.....	....	....	No studies of vital capacity
S. L.	35	Rheumatic heart disease, mitral stenosis, auricular fibrillation	8/25/27	9.9	5.5	3,040	1,725	43	1,650	4.4	−25	
			8/28/27	12.8	4.8	.....	1,675	45	1,675	0.0	0	
			9/ 1/27	13.4	10.1	.....	1,750	42	1,650	5.7	−25	
			9/ 4/27	13.3	11.3	.....	1,700	44	1,700	0.0	+75	
			9/ 8/27	14.0	9.0	.....	1,650	46	1,625	1.5	0	
A. W.	30	Rheumatic heart disease, mitral stenosis	9/ 9/27	14.0	4.7	3,060	600	80	550	8.3	0	
			9/12/27	14.9	11.0	.....	600	80	525	12.5	+50	
			9/15/27	11.9	8.6	.....	725	76	700	3.5	0	
			9/19/27	10.7	8.0	.....	850	72	700	17.6	0	
			9/23/27	10.4	4.7	.....	700	77	600	14.3	0	
			9/27/27	10.5	7.6	.....	950	69	950	0.0	0	
			10/ 1/27	17.9	8.7	.....	1,050	65	925	11.9	+75	
R. W.	63	Arteriosclerotic heart disease	9/19/27	6.0	12.5	4,300	1,275	70	1,225	3.9	0	
			9/23/27	6.8	11.1							
			9/27/27	4.1	13.4	.....	1,800	58	1,800	0.0	−25	No orthopnea of necessity

P. L.	41	Rheumatic heart disease, mitral stenosis, auricular fibrillation	11/ 3/27	20.1	11.8	4,450	1,600	64	1,300	18.8	0	
			11/ 6/27	22.0	15.4	.....	1,500	71	1,500	0.0	+25	
			11/10/27	19.0	18.4	.....	1,700	62	1,525	10.3	+25	
			11/14/27	18.9	15.6	.....	1,825	58	1,675	8.2	0	
			11/17/27	13.8	16.2	.....	1,600	64	1,500	6.3	−25	
			11/24/27	20.8	19.0	.....	1,675	63	1,500	10.4	+50	
			11/28/27	22.1	12.5	.....	1,650	63	1,525	7.6	−25	
			12/ 6/27	10.7	15.6	.....	1,450	68	1,300	10.3	+50	
			12/12/27	19.7	21.7	.....	1,250	72	1,000	20.0	+50	
			12/16/27	20.5	17.7	.....	1,200	73	1,050	12.5	+50	
			12/20/27	23.7	19.8	.....	1,225	73	1,100	10.2	−25	
			12/28/27	16.3	18.2	.....	1,125	75				
H. B.	53	Arteriosclerotic heart disease	12/16/27	12.9	6.7	5,180	1,725	67	1,450	16.0	+250	
			12/20/27	7.6	8.9	.....	2,250	57	2,075	7.8	+25	
			12/24/27	11.6	9.1	.....	2,375	54	2,325	2.1	−25	
			12/28/27	9.3	9.7	.....	2,350	55	2,250	4.3	−50	
			1/ 2/28	5.4	6.8	.....	2,725	47	2,575	5.5	+50	No orthopnea of necessity
E. S.	68	Arteriosclerotic heart disease, auricular fibrillation	12/21/27	7.2	8.2	4,525	2,875	37	2,750	4.3	+25	
			12/26/27	8.3	8.4	.....	3,000	34	2,850	5.0	0	
H. W.	60	Arteriosclerotic heart disease, auricular fibrillation	12/31/27	7.9	10.5	4,250	.....	..	.....	.....	.....	No measurement of vital capacity because of coughing
			1/ 2/28	5.4	9.7	.....	2,150	49	1,950	9.3	+50	
			1/ 6/28	7.0	8.9	.....	2,150	49	2,125	1.2	+25	
			1/ 9/28	9.1	10.8	.....	2,075	51	1,950	6.0	+100	
			1/13/28	8.2	9.7	.....	2,150	49	2,050	4.7	−50	
D. B.	72	Arteriosclerotic heart disease, angina pectoris	1/ 2/28	12.5	12.1	.....	1,200	..	1,050	12.5	+50	
J. R.	62	Arteriosclerotic heart disease, auricular fibrillation, angina pectoris	1/ 4/28	15.9	11.3	4,900	1,700	65				
			1/ 7/28	14.7	13.0	.....	1,700	65				
			1/10/28	7.0	6.1	.....	2,050	58				
			1/15/28	1.1	9.5	.....	2,250	54	2,250	0.0	−50	No orthopnea of necessity
A. P.	62	Arteriosclerotic heart disease, auricular fibrillation	1/ 4/28	29.2	11.8	4,225	1,750	59	1,650	5.7	−50	
			1/ 6/28	17.7	18.1	.....	1,825	57	1,700	6.9	+25	
			1/ 9/28	15.3	12.3	.....	2,025	52	1,925	4.9	−25	
			1/13/28	15.3	9.6	.....	2,000	53	2,000	0.0	−25	
			1/18/28	10.9	11.2	.....	2,100	50	1,975	6.0	−75	
			1/22/28	7.1	12.6	.....	2,000	53	1,825	8.8	+25	
			1/25/28	7.9	12.5	.....	2,200	48	1,975	10.2	−75	
			2/ 5/28	12.0	9.1	.....	1,975	53	1,800	8.9	−25	
J. D.	65	Arteriosclerotic heart disease, auricular fibrillation	6/27/28	7.7	15.1	4,300	2,150	50	1,900	11.6	+100	
			7/ 2/28	5.2	12.7	.....	2,450	43	2,100	14.3	+150	

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Summary of Observations on Venous Pressure, Vital Capacity of the Lungs, and Degree of Orthopnea—Continued

Subject	Age	Diagnosis	Date	Venous Pressure, Cm. of Water	Occipitial Protuberance to Right Auricle, Cm.	Vital Capacity						Comment
						Estimated Normal, Cc.	In Orthopneic Position, Cc.	Reduction from Estimated Normal, per Cent	In Recumbent Position with Head Flat, Cc.	Decrease from Orthopneic Position, per Cent	Change on Elevating Head, Cc.	
M. R.	21	Rheumatic heart disease, mitral stenosis, auricular fibrillation	6/28/28	20.7	13.0	3,240	1,750	46	1,475	15.7	+25	
			7/ 3/28	9.6	15.0	.....	2,100	35	1,850	11.9	−100	
			7/ 7/28	8.2	20.0	.....	2,225	31	2,100	5.6	−100	No orthopnea of necessity
C. W.	57	Arteriosclerotic heart disease, coronary thrombosis	7/ 3/28	16.5	12.0	.....	1,050	..	1,050	0.0		
J. B.	47	Hypertensive heart disease	7/ 3/28	5.8	9.5	.....	2,075	..	1,825	12.0	0	
M. B.	36	Rheumatic heart disease, mitral stenosis, auricular fibrillation	7/ 7/28	9.2	19.3	3,200	1,650	48	1,600	3.0	+50	
F. M.	46	Rheumatic heart disease, mitral stenosis, auricular fibrillation	7/ 7/28	23.0	15.5	4,300	1,150	73	875	23.9	+25	Venesection, 400 cc. on 7/12/28
			7/10/28	21.4	22.0	.....	975	78	900	7.7	+50	
			7/16/28	12.0	12.5	.....	1,850	57	1,600	13.5	+25	No orthopnea of necessity
M. I.	15	Rheumatic heart disease, mitral stenosis	1/11/29	23.5	15.8	.....	.....	..	.....	....	....	No studies of vital capacity
M. A.	46	Hypertensive heart disease	1/17/29	20.0	13.5	3,140	1,400	55	1,250	10.7	+50	
C. B.	41	Rheumatic heart disease, mitral stenosis, auricular fibrillation	1/25/29	18.2	13.5	3,080	1,310	58	1,250	4.6	+50	
			1/28/29	18.5	8.5	.....	1,190	62	950	20.0	+150	
			1/30/29	20.2	13.3							
			2/ 4/29	16.7	8.8	.....	1,400	54	1,200	14.3	+25	
			2/ 7/29	16.3	15.8	.....	1,500	51	1,475	1.7	0	
Average								58.4*	.....	8.3*	+14	

* Does not include readings taken after disappearance of orthopnea of necessity.

COMMENT

In addition to the evidence presented, we believe that certain clinical phenomena and the following observations of other investigators support the venous pressure theory of orthopnea. Hill [19] stated that any increase in general venous pressure caused a slowing of cerebral blood flow. Wolff and Blumgart [25] observed in animals that a definite slowing of the velocity of intracranial blood flow resulted from elevation of the intracranial cerebrospinal fluid pressure. A rise in cerebrospinal fluid pressure is accompanied by an increase in cerebral venous pressure because the skull is a closed cavity without elasticity. The pressures of the cerebrospinal fluid and venous blood must closely approach each other. It therefore may be assumed that Wolff and Blumgart would have observed the same slowing of velocity of blood flow if the cerebral venous pressure had been raised directly instead of indirectly by increasing the intracranial pressure. This work therefore demonstrates the validity of the basic assumption of the venous pressure theory of orthopnea, namely, that an increased general and cerebral venous pressure diminishes the cerebral capillary blood flow.

Salathé [26] applied a tambour to the fontanel of an infant 6 weeks old and observed that on his placing the child in a vertical position with the feet down the intracranial pressure fell, and that on his turning the child to a posture with the feet up the pressure rose. Brissaud and Franck [27] observed the same changes of pressure in a patient in whom a large portion of the skull had been removed. Hill [11] found that the intracranial pressure of a patient who had been trephined was negative while the man sat upright, but became positive as soon as the head was bent down toward the knees or on any expiratory effort. All these observations indicate that in man intracranial pressure and therefore cerebral venous pressure is diminished by changing from the recumbent to the sitting position.

It is well recognized that, in patients with myocardial failure, cyanosis of the face and lips increases in the recumbent position or may appear only in that position. It is probable that this cyanosis is due in large part to retarded capillary blood flow and stagnation anox-

25. Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

26. Salathé, A.: Recherches sur le mecanisme de la circulation dans la cavite cephalo-rachidienne, Trav. du labor. de M. Marey **2**:345, 1876.

27. Brissaud, E., and Franck, F.: Inscription des mouvements d'expansion et de rétrait du cerveau chez une femme présentant une vaste perte de substance du parietal gauche, Trav. du labor. de M. Marey **3**:137, 1877.

emia.[28] Since such alterations occur in the superficial capillaries in the recumbent position, it is reasonable to suppose that comparable changes take place simultaneously in the capillaries about the respiratory center. In both locations, the decreased capillary blood flow undoubtedly results from the local increase in venous pressure in the recumbent position. This together with the observed correlation between the height of venous pressure and the degree of orthopnea suggests that in patients with myocardial failure the elevated position provides relief mainly by releasing the respiratory center from the effects of increased venous pressure. The correlation between the height of venous pressure and the degree of orthopnea suggests further that these patients at all times tend to maintain an elevation which is sufficient to keep the respiratory center above the meniscus of the column of venous blood extending upward from the right auricle. In this way, the flow of blood in the capillaries in the region of the respiratiory center is kept as efficient as is possible with the existing myocardial failure.

It is a common clinical observation that in patients with congestive failure the jugular veins are engorged as high as the angle of the jaw in the recumbent position, but when the upright posture is assumed the column of blood is visible for only a short distance above the clavicle. Similar changes occur when the head is flexed on the thorax in the recumbent position. This indicates that any elevation of the head reduces the cerebral venous pressure and therefore the venous pressure about the respiratory center. This observation and the relief experienced in the recumbent position when the head is elevated strongly support the venous pressure theory of orthopnea. Of all the theories of orthopnea, only the venous pressure theory and Sahli's[10] hypothesis of the effect of gravity on cerebral venous congestion can explain the relief experienced by the patient on flexing the head on the thorax. As the position of the thorax and abdomen is unchanged when the head is elevated, the increased comfort cannot be due to an alteration in the amount of blood in the lungs. Similarly, the relief cannot be attributed to increased efficiency of the abdominal and thoracic accessory muscles of respiration, to changes in reserve air, middle capacity or vital capacity of the lungs, or to alterations in lung expansion.

It may be contended that according to our hypothesis a normal person should suffer from intense dyspnea due to increased venous pressure when the head is held lower than the rest of the body. The work of Wolff and Blumgart[25] indicates, however, that, in such subjects, the increased venous pressure is balanced by either an increased arterial pressure or arteriolar dilatation. In either case, the normal pressure gradient in the capillaries would be maintained. In patients

28. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine **2**:1, 1923.

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with circulatory failure, however, vasodilatation is already present, and an increase in arterial pressure in all probability does not take place. The cyanosis of the face observed in normal persons when the head is held lower than the rest of the body may well be related to the type of cyanosis observed by Goldschmidt and Light [29] in which no change in the venous oxygen unsaturation took place.

The evidence which we have accumulated from our own observations and from the investigations of others is in accord with the venous pressure theory of orthopnea. It should be recognized, however, that some of the factors considered as of primary importance by other investigators undoubtedly contribute to the relief experienced in the sitting position. The more complete oxygenation of the blood in the lungs in the upright as compared with the recumbent posture [5] must aid in securing the relief experienced by the patient in the former position. Furthermore, in those patients who show an important increase in vital capacity of the lungs on changing from the recumbent to the sitting posture,[7] this increase must be responsible, in part, for the comfort obtained. In patients with ascites,[10] the upright position undoubtedly affords relief partly because this position facilitates diaphragmatic movements. We believe, however, that in all patients with congestive heart failure and increased venous pressure, the relatively low cerebral venous pressure obtained in the sitting position is the primary factor in reducing the respiratory discomfort.

SUMMARY

1. A new theory of the mechanism of orthopnea in uncomplicated myocardial failure of the congestive type is offered. This theory is based on the fact that increased cerebral venous pressure diminishes intracranial blood flow, thereby favoring increased anoxemia of the respiratory center. Accordingly, a patient with myocardial failure and increased venous pressure always tends to maintain an elevation in bed sufficient to keep the respiratory center above the meniscus of the column of venous blood extending upward from the right auricle. In the upright position, the pressure in the veins about the respiratory center is kept more nearly normal than in any other position, and the blood flow in the capillaries feeding these veins is increased to the maximal limit set by the existing myocardial failure.

2. In order to test the validity of the hypothesis, eighty-two comparisons of the height of venous pressure and the degree of orthopnea were made in twenty-two patients with uncomplicated myocardial failure of the congestive type.

29. Goldschmidt, S., and Light, A. B.: A Cyanosis, Unrelated to Oxygen Unsaturation, Produced by Increased Peripheral Venous Pressure, Am. J. Physiol. **73**:173, 1925.

3. A parallelism between the two measurements was observed. In general, it was found that the higher the venous pressure, the greater was the orthopnea.

4. When orthopneic patients were placed in the recumbent position with the head flat, simple elevation of the head by flexion of it on the thorax produced, almost without exception, conspicuous diminution of respiratory distress. This procedure favors diminution of the cerebral venous pressure, but has no significant effect on the vital capacity of the lungs. These observations strongly support the venous pressure theory of orthopnea.

5. In striking contrast to the definite correlation between the venous pressure and the degree of orthopnea, no such correlation was observed between the percentage reduction of the vital capacity of the lungs and the degree of orthopnea.

6. The extent of the diminution of the vital capacity of the lungs does not appear to be an important factor in determining the degree of elevation which gives the patient maximum relief.

7. Orthopnea of necessity was observed in patients in whom the vital capacity of the lungs was not significantly increased by changing from the recumbent to the sitting position.

8. Although various factors contribute to the relief experienced in the sitting position, observations indicate that in all patients with congestive heart failure and increased venous pressure, the relatively low cerebral venous pressure in the upright posture is the primary factor in reducing the respiratory discomfort.

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THE BLOOD IN LIPOID NEPHROSIS

WITH SPECIAL REFERENCE TO THE ABSENCE OF ANEMIA *

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ROCHESTER, MINN.

The most striking feature in lipoid nephrosis, aside from the edema, is the patient's pallor, which suggests the presence of considerable anemia. Examination of the blood, however, often shows that the erythrocytes and the hemoglobin are normal. For this reason, statistical data on this point were assembled. It is well known that in another form of renal disease, chronic glomerular nephritis, secondary anemia is frequently a prominent feature; in fact, this has been shown to be of accurate prognostic value.[1]

It is generally accepted that pure lipoid nephrosis is a definite clinical entity, although it occurs rarely. It is much more common to observe cases of diffuse nephritis in which the nephrotic or tubular element is predominant. Müller [2] introduced the term "nephrosis" in 1905 as representing a degenerative renal lesion, in contradistinction to nephritis, in which there is an infectious and usually a glomerular process. However, Aschoff [3] and others believed that an inflammatory process is always present in renal disease, and such writers as Löhlein,[4] Kollert,[5] and Elwyn [6] stated that nephrosis begins as acute glomerular nephritis. They agreed that this process may later subside and give

* Submitted for publication, Aug. 12, 1929.

* From the Division of Medicine, the Mayo Clinic.

1. Brown, G. E., and Roth, Grace M.: Prognostic Value of Anemia in Chronic Glomerular Nephritis, J. A. M. A. **81**:1948 (Dec. 8) 1923.

2. Müller, Friedrich: Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch. **9**:64, 1905.

3. Aschoff, quoted by McElroy, J. B.: Nephroses, J. A. M. A. **89**:940 (Sept. 17) 1927.

4. Löhlein, M.: Ueber die Entzündlichen Veränderungen der Glomeruli der Menschlichen Nieren und ihre Bedeutung für die Nephritis, Leipzig, S. Herzel, 1907, p. 98.

5. Kollert, V.: Das Problems der Lipoidnephrose, Klin. Wchnschr. **5**:441, 1926.

6. Elwyn, Herman: The Pathogenesis of Lipoid Nephrosis, Arch. Int. Med. **38**:346 (Sept.) 1926.

way to almost pure nephrosis, but that glomerular inflammatory lesions may always be found on pathologic examination in such cases.

It is also generally conceded that in cases of lipoid nephrosis metabolism is profoundly disturbed. This has been especially emphasized by Epstein; the condition is indicated by hypoproteinemia, hyperlipemia and marked generalized edema, which probably is not entirely of renal origin. Chronic diseases, as a rule, are accompanied by anemia which is secondary to the disease process and frequently of significance in the consideration of the patient. In view of the marked pallor, the possibility of previous glomerular involvement, the profound metabolic disturbances and the frequent chronicity of the disease, anemia might possibly be expected in cases of lipoid nephrosis.

HISTORICAL DATA

Many statements have been made concerning the blood counts in lipoid nephrosis, but these have been substantiated with few figures. Munk,[7] who expressed the belief that most cases of nephrosis are syphilitic in origin, described the clinical picture as one of marked anemia, edema, oliguria, albuminuria, casts and low blood pressure. Volhard [8] stated that investigations of his colleague, Keller, have shown that in the early stage of nephrosis, hydremia does not exist, but that, on the contrary, the blood is abnormally concentrated. The erythrocyte count is at the upper limit of normal, and the viscosity may be increased. He expressed the belief that with the onset of diuresis and the disappearance of edema, hydremia develops. The erythrocyte count falls and may decrease to the extent of from 1,000,000 to 2,000,000 in each cubic millimeter; at this point, the anemia becomes apparent for the first time. Linder, Lundsgaard, Van Slyke and Stillman [9] reported on the blood counts in five cases of subchronic glomerular nephritis of the nephrotic type and on two cases of pure nephrosis. In the latter cases, the erythrocyte count was normal, whereas in the five mixed cases of nephrosis definite anemia was shown. Brown and Rowntree,[10] following a study of nine cases of pure and mixed nephrosis, stated: "Anemia is not marked or constant in nephrosis. Our data show that in five of the nine cases the hemoglobin values and the values obtained by the

7. Munk, Fritz: Klinische Diagnostik der degenerativen Nierenerkrankungen, Ztschr. f. klin. Med. **78**:1, 1913.

8. Volhard, Franz: Die doppelseitigen hämatogenen Nierenkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918.

9. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, J. Exper. Med. **39**:921, 1924.

10. Brown, G. E., and Rowntree, L. G.: Blood Volume in Edema of Glomerular Nephritis and Nephrosis, Arch. Int. Med. **41**:44 (Jan.) 1928.

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hematocrit were normal; in the remaining four cases there was a mild degree of anemia. . . . The mean hemoglobin in grams per cent was 15.7 and the mean percentage of cells as ascertained by the hematocrit was 37.5." In summary they concluded: "In cases of nephrosis with edema, approximately 50 per cent do not show anemia, the remainder show mild grades of anemia." The criteria used in these cases were not so rigid as those employed in our study. Albutt,[11] in a clinical lecture on renal dropsy, remarked: " . . . remembering that these patients are always anemic . . . ." Kaufmann and Mason [12] remarked: "There is a moderate but progressive anemia in this disease." Concerning nephrosis Epstein [13] said: "A certain degree of dilution develops which is occasionally more marked in the early than late stages [possibly during the acute glomerular stage according to Elwyn,[6] Löhlein [4] and Kollert [5]]. The red blood cells become diminished in numbers and the hemoglobin falls." Altnow [14] cited a case of nephrosis in which the "blood picture remained normal despite a constant loss of albumin in the urine." Boyd [15] mentioned that moderate but progressive anemia is present in nephrosis. Lewis and Scriver [16] stated that the skin takes on an extreme pallor which is out of proportion to the blood count. Elwyn [17] stated that in lipoid nephrosis formed elements of the blood show little change: "Moderate anemia is usually present. The red blood cells are usually around 4,000,000 for each cubic millimeter. The hemoglobin averages from 70 to 80 per cent. With reabsorption of the edema fluid, the blood is temporarily diluted and the anemia seems to increase. There is no change in the leukocytes." Elwyn did not give actual counts nor did he give the number of cases reviewed, or the method used in the determination of hemoglobin.

In the study of fourteen children with lipoid nephrosis, Schwartz and Kohn [18] reported: "The anemia of this disease is usually of a mild

11. Albutt, T. G.: A Clinical Lecture on Renal Dropsy, Brit. M. J. **2**:395, 1928.

12. Kaufmann, Joseph, and Mason, Edward: Nephrosis: A Clinical and Pathologic Study, Arch. Int. Med. **35**:561 (May) 1925.

13. Epstein, A. A.: Clinical Types of Chronic Parenchymatous Nephritis: Their Treatment and Results, M. Clin. North America **4**:145, 1920.

14. Altnow, H. O.: The Evolution of Nephritis; Its Prognosis and Treatment: II. Prognosis in Nephritis, Minnesota Med. **10**:231, 1927.

15. Boyd, William: Nephrosis, Canad. M. A. J. **16**:349, 1926.

16. Lewis, D. S., and Scriver, W. deM.: The Response of Chronic Nephrosis to Parathyroid and Thyroid Medication, Ann. Int. Med. **2**:66 (July) 1928.

17. Elwyn, Herman: Nephritis, New York, The Macmillan Company, 1926, p. 194.

18. Schwartz, Herman, and Kohn, J. L.: Studies of Nephritis in Children: I. Nephrosis, Am. J. Dis. Child. **24**:125 (Aug.) 1922.

secondary type and it is only at the end of the disease that the hemoglobin may drop below 50 per cent, the red cells rarely falling below 3,000,000, there not being much difference before, during or after disappearance of the anasarca." From this series of fourteen children they concluded that the children often looked very anemic, but that the absolute anemia was not very great. Davison and Salinger,[19] in a study of twenty-six cases of nephrosis in children, stated: "The hemoglobin content was over 85 per cent (Sahli) in only two patients. The average was 69 per cent with minimal and maximal values of 52 per cent and 95 per cent." In this group were cases in which glomerular lesions were obvious and several in which there was severe infection, so that these values are not conclusive. Marriott[20] remarked: "There is a secondary anemia . . . A high protein diet leads to a disappearance of the anemia." In another paper,[21] he stated: "Secondary anemia rapidly develops. Not only are the red blood cells and the hemoglobin diminished but the serum protein and the blood mass are diminished also." Clausen[22] stated that in children with nephrosis, moderate but severe anemia always occurs. He added: "The capillaries of the nail beds show at most the changes due to anemia. . . . Transfusion is indicated for anemia and also has been of benefit in temporarily increasing protein of the blood." It must be remembered that in children with nephrosis, accessory nasal sinus infection[22] and pneumococcic peritonitis[10] are often prominent features, and in the presence of active infection the blood count and hemoglobin may be altered by these factors alone.

One would conclude from the foregoing data that the adult with nephrosis is usually pale or pasty in appearance, but that the blood is only slightly, if at all, anemic. In the child, however, the anemia is more marked and may in fact be so progressive as to warrant transfusion of blood.

Material Studied and Criteria for Selection.—In the period from 1921 to 1929 there were registered at the Mayo Clinic twenty-five cases of pure lipoid nephrosis and twenty-six cases of the mixed form in

19. Davison, W. C., and Salinger, Robert: Tubular Nephritis (Nephrosis) in Children and Its Relationship to Other Forms of Nephritis, Bull. Johns Hopkins Hosp. **41**:329, 1927.

20. Marriott, W. McKim: Nephritis: Some Newer Viewpoints Concerning Its Nature and Treatment, Northwest Med. **24**:472, 1925.

21. Marriott, W. McKim: Newer Knowledge Concerning Nephritis, Illinois M. J. **51**:120, 1927.

22. Clausen, S. W.: Parenchymatous Nephritis: I. As a General Systemic Disorder, Am. J. Dis. Child **29**:581 (May) 1925; II. Infection of the Paranasal Sinuses as Etiology, ibid. **29**:587 (May) 1925.

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which the nephrotic element predominated. Epstein,[23] in describing nephrosis, stated: "We have therefore a disease of gradual onset, chronic course, characterized by edema, anasarca and effusion in the serous cavities, by a marked albuminuria with or without casts, and the absence of any blood in the urine, by the absence of hypertension and cardiac hypertrophy; a reduction in the protein content of the blood, inversion of the albumin-globulin ratio and by the increase of the blood, lipoids and finally by a reduction in the basal metabolism." This is the classic picture of so-called chronic lipoid nephrosis which is a rare disease. In selecting the group of pure cases of nephrosis in the present work, we have used the following criteria: (1) edema, graded 2, which has persisted for at least a month; (2) absence of any hematuria except possibly an occasional erythrocyte in the urine; (3) albuminuria, graded 2; (4) systolic blood pressure of less than 140, and diastolic, 90, measured in millimeters of mercury; (5) blood urea of less than 40 mg. for each 100 cc.; (6) phenolsulphonphthalein return of at least 40 per cent in two hours, and (7) normal fundus oculi save for edema or lipemia retinalis. Cases of toxic nephrosis such as are seen in mercuric chloride poisoning have not been included in this study.

In most of the cases, quantitative studies of the proteins and the lipoids in the blood were made, and hypoproteinemia and hyperlipemia were found to be present. In cases in which the albumin-globulin ratio was studied, it was found to be inverted.

The first group of twenty-five cases of pure nephrosis fit in with these criteria; therefore, for the sake of brevity, the actual observations in each case in this group will not be recorded here.

The second group included twenty-six cases of chronic diffuse nephritis of the nephrotic type. They were separated from the first group because in various ways they did not satisfy the criteria for pure nephrosis, but at the same time they displayed clinical pictures which were definitely nephrotic.[24]

The methods of determining the hemoglobin in these cases were as follows:

1. The Dare method, which is reported in percentages of hemoglobin. Chart 1 shows the relationship between the readings of hemoglobin by the Dare and the Palmer-Haldane methods. This figure shows that a reading of 70 per cent, or above, by the Dare method, is a normal value for hemoglobin, and 70 per cent has been taken as the lower limit of normal in the present work.

23. Epstein, A. A.: Clinical Course and Therapeutic Management of Chronic Nephrosis, M. Clin. North America **5**:1067, 1922.

24. After careful observation, diagnosis of these cases was made by Dr. N. M. Keith and Dr. E. G. Bannick.

2. In many of the cases, the more accurate method of Osgood and Haskins [25] has been used. The normal value for the acid hematin by this method has been shown by Osgood [26] to be 15.76 Gm. for each 100 cc. of blood, in the male. Haden,[27] using the oxygen capacity of the blood as a measure of the hemoglobin content, found it to average 15.6 Gm. in each 100 cc. of blood in normal persons of both sexes. An erythrocyte count of 4,000,000, or more, has been taken as normal.

RESULTS

The results of the study of the blood count in the two groups of cases have been summarized. In the twenty-five cases of pure nephrosis, the mean erythrocyte count with the probable error was 4,350,000 ± 50,000, with extremes of 3,310,000 and 5,490,000 for each cubic millimeter in a total of ninety-eight counts. The mean value for hemoglobin for the same group was 75.4 per cent (Dare), which again is well above the normal limits. The extreme variations in this group were 62 and 95 per cent. The much more accurate acid hematin method of Osgood and Haskins in twenty-one of these cases in which it was done showed a mean value of 15.55 Gm. in each 100 cc., which corresponds well with the normal accepted value of 15.76 Gm. in each 100 cc. Of these twenty-five cases of pure nephrosis, one case only showed definite anemia with both the Dare and the Osgood-Haskins determinations for hemoglobin. The remainder of the cases showed a normal value by one or both methods. The leukocyte count was normal in almost every instance. In occasional cases, unexplained moderate leukocytosis was present.

In the second group, comprising twenty-six cases of chronic nephritis of the nephrotic type, the mean erythrocyte count with the probable error was 3,845,000 ± 63,000, with extremes of 2,150,000 and 5,100,000 for each cubic millimeter. The mean hemoglobin value was 66.67 per cent (Dare) with extremes of 38 and 89 per cent, and the mean value for the acid hematin in nineteen of the twenty-six cases was 13.3 Gm. for each 100 cc. Nineteen (73 per cent) of the patients showed definite evidence of anemia. The leukocyte count was perhaps slightly higher in this group than in the first group, which probably can be explained by the fact that acute and chronic infection was much more frequently found in the mixed than in the pure types of nephrosis. The contrast in the results of the two groups may be noted in chart 2.

25. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107, 1923.

26. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index, and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926.

27. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923.

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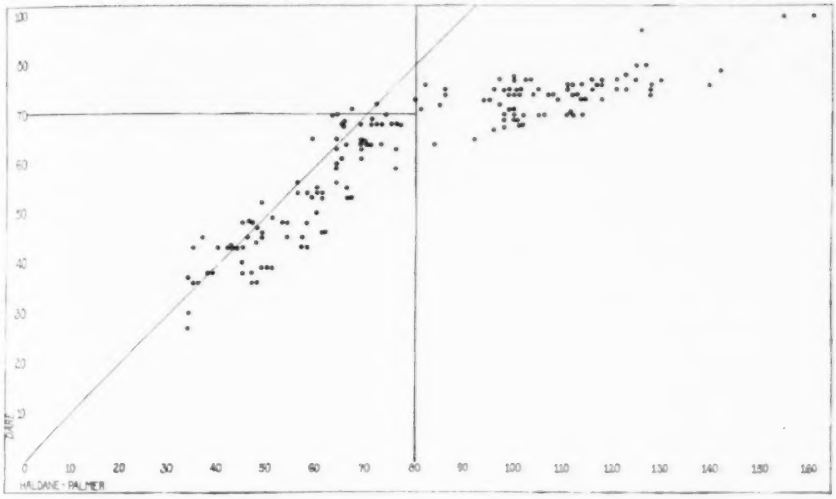

Chart 1.—Relationship of Dare and Haldane-Palmer estimations of hemoglobin.

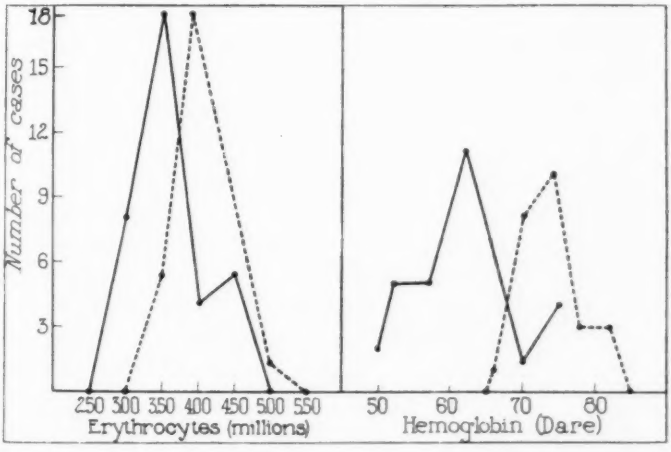

Chart 2.—Comparison of erythrocytes and hemoglobin in mixed nephrosis and pure nephrosis; the dash line indicates mixed nephrosis; the dotted line, pure nephrosis.

BLOOD VOLUME

The effect of edema and diuresis on the blood volume in renal disease has been widely discussed. The presence of marked edema and the frequent occurrence of anemia in nephritis have led certain observers to conclude that hydremia or edema of the blood is associated with dilution anemia. Fluctuations in the concentration of the plasma protein or other constituents of the blood during the course of the disease have been used as a measure of the amount of dilution of blood. Linder, Lundsgaard, and Van Slyke [28] and others have shown that variations in the concentration of the plasma protein are due to absolute variations in this substance and not to variations in the blood volume and plasma volume.

In three cases in each of the two groups the blood volume was studied by the dye method of Keith, Rowntree and Geraghty.[29] It was realized, as Bennhold [30] pointed out, that congo red, which it used in this determination, disappears rapidly from the circulation in cases of pure nephrosis because of elimination through the kidney. Brown and Rowntree have shown, however, that the rate of disappearance of the dye in pure nephrosis averages only 1.5 per cent more than the normal within the three, four and six minute intervals following injection. This is well within the limits of error and indicates that such determinations are probably fairly accurate in this disease during this short interval.

The blood volume in the six cases has been calculated on the basis of the body weight during the period of edema and in the edema-free state, which are designated, respectively, as the uncorrected and the corrected body weight. The surface area has been calculated according to the DuBois standards, the corrected body weight only being used. In the three cases of pure nephrosis, the blood volume according to the uncorrected body weight was less than the normal mean of 89.1 cc. for each kilogram.[10] On the basis of corrected body weight, however, the values are all above this normal mean value, but are close enough to this mean to constitute normal values. The volume of plasma for each kilogram of body weight was normal in one case, and considerably increased in the other two. In one of the three cases, at the time of examination, definite, although slight, anemia was present, whereas in the other two, the values for hemoglobin were normal. At the same time, this anemic

28. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887, 1924.

29. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

30. Bennhold, H.: Ueber die Absorptionsfähigkeit der Serumkolloide tubulär Nierenkranker gegenüber Farstoffen, Ztschr. f. d. ges. exper. Med. **49**:71, 1926.

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patient showed an increased percentage of plasma in the plasma-cell relationship as shown by the hematocrit.

In two of three cases of mixed nephrosis, the blood volume for each kilogram of corrected body weight was distinctly elevated. In one of these, the elevation was representative of relative and absolute increase in the plasma volume, and in the other it was the result of an absolute increase in the total volume of the blood, the cell-plasma relationship remaining approximately normal. In both of these cases there was considerable anemia at the time of the examination, as shown by the acid hematin values of 11.1 and 11.9 Gm. for each 100 cc. The remaining case showed only moderate diminution in volume and a normal value for hemoglobin.

In three cases, blood volume studies were made before and after diuresis had occurred.

TRANSITION OF NEPHROSIS INTO GLOMERULAR NEPHRITIS (ILLUSTRATIVE CASE)[31]

The patient in this case fulfilled all the criteria for the diagnosis of pure chronic lipoid nephrosis. Within a short time, chronic glomerular nephritis developed, and the outcome was fatal. From the standpoint of the blood count alone, the development in this case was dramatic and showed the close relationship between anemia and glomerular disease.

A man, aged 32, presented himself at the Mayo Clinic on May 16, 1926, with a history of four months of general anasarca of undetermined origin. A diagnosis of pure nephrosis was made (table 1). Edema of the lower extremities, graded 2, ascites, graded 2, and slight hydrothorax were present. The urine contained albumin, graded 2, and many casts, but erythrocytes were not found at any time. The systolic blood pressure was 120, and the diastolic, 90, measured in millimeters of mercury. The basal metabolic rate was —12, the blood urea was 37 mg. for each 100 cc., the phenolsulphonphthalein return in two hours was 60 per cent, the plasma protein 4.06 Gm. for each 100 cc., and the cholesterol of the blood was 344 mg. for each 100 cc. The erythrocytes numbered 4,500,000; the hemoglobin was 70 per cent (Dare) and 17.5 Gm. for each 100 cc. (Osgood and Haskins). The patient lost weight, decreasing from 158 pounds on entrance to 113 pounds on dismissal, largely owing to disappearance of the edema following treatment with a diet low in salt and in protein and intensive treatment by ammonium chloride and merbaphen. The blood count on dismissal was about the same as on admission, and the patient appeared to be in good condition.

The patient returned in October, 1926, for reexamination. At this time, nine months after the onset, the blood pressure was slightly elevated (158 systolic and 115 diastolic), and there was early evidence of renal insufficiency, with an output of phenolsulphonphthalein of 30 per cent in two hours, blood urea 52 mg. for

31. This case resembles a case reported by E. H. Mason (The Life History of a Case of Nephrosis, Internat. Clin. **50**:163, 1926) and one reported by Brown and Rowntree.

each 100 cc. and creatinine of 3.2 mg. for each 100 cc. The results of the examination of the fundus oculi were still negative. The erythrocytes numbered 3,100,000, and the hemoglobin was 68 per cent (Dare). The patient felt reasonably well. There was, however, definite evidence of glomerular involvement.

Five months later, the patient returned again because of headaches, blurred vision, vomiting and loss of weight. He was obviously in poor condition and was anemic. He was placed in the hospital, where marked renal impairment was noted. The blood urea was 221 mg. for each 100 cc., the systolic blood pressure was 210 and the diastolic 140; the phenolsulphonphthalein return was 5 per cent. Ophthalmic examination showed anemic disks with mild edema of the retina surrounding them and extending to the macular regions. There were a few small hemorrhages, and the examiner concluded that the change indicated early first stage of glomerular nephritis. The erythrocytes numbered 2,250,000, and the hemoglobin was 48 per cent (Dare), evidence of marked secondary anemia. Four days after admission, the patient died. Necropsy showed chronic diffuse nephritis.

TABLE 1.—*Transition from Pure Nephrosis to Glomerular Nephritis: Effect on Blood Count*

Date	Weight, Lb.	Edema, Grade	Blood Pressure		Basal Metabolic Rate	Erythrocytes, Millions	Hemoglobin		Blood Urea, Mg. for Each 100 Cc.	Blood Creatinine, Mg. for each 100 cc.	Return of Phenolsulphonphthalein, Per Cent	Erythrocytes in Urine	Blood Cholesterol, Mg. for Each 100 Cc.	Plasma Protein, Gm. for Each 100 Cc.
			Systolic	Diastolic			Per Cent (Dare)	Gm. for Each 100 Cc. (Osgood and Haskins)						
5/16/26*	72.2	Legs, 2 Ascites, 2	120	90	—12	4.28	70	17.5	37	1.4	60	None	284	4.06
6/17/26	51.3	None	118	70	—19	4.57	74	16.2	15	....	..	None	344	4.3
10/18/26†	61.6	Ankles, 1	158	115	....	3.10	68	....	52	3.7	30	None	327	....
3/ 4/27‡	61.8	Face, 2 to 3	210	140	....	2.25	48	....	221	11.0	5	Many	311	5.8

* Fundus oculi not examined; diagnosis, pure nephrosis.
† Fundus oculi normal; diagnosis, mixed nephrosis.
‡ Blurred vision, headaches, vomiting; first stage retinitis of glomerular nephritis; chronic diffuse nephritis diagnosed. Chronic diffuse nephritis was found at necropsy.

COMMENT

Although glomerular involvement in nephritis is not always associated with anemia, it has been shown that if renal insufficiency supervenes, anemia almost always develops. One would expect, therefore, to find anemia absent in cases of nephrosis without glomerular involvement; that is, in cases of pure nephrosis. That such is actually the case is illustrated by the present study of twenty-five cases of pure nephrosis, in only one of which there was anemia. A follow-up study of this patient revealed that within six months after his blood was last studied at the clinic, definite signs of glomerular nephritis had developed. The cases of mixed nephrosis stand in distinct contrast to those of pure nephrosis. Of the twenty-six mixed cases, nineteen (73 per cent) showed evidence of definite anemia, two thirds of which presented evidence of renal insufficiency; all but one of the remaining third showed mean values for hemoglobin that were approximately the

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average in the cases of mixed nephrosis (66.67 per cent Dare), as shown in table 2. These figures show that glomerular involvement as it occurs in cases of mixed nephrosis is usually accompanied by slight anemia. With the development of renal insufficiency, anemia is definite.

In a study of 185 cases of chronic glomerular nephritis in 1922, Brown and Roth [32] divided the cases into two groups, those in which anemia was present and those in which it was not present. In the 105 cases in which anemia was present, the average erythrocyte count was 3,310,000 and the average value for hemoglobin was 56 per cent

TABLE 2.—*Analysis of Anemia in Cases of Mixed Nephrosis*

Case	Renal Insufficiency, Grade	Erythrocytes, Millions (Mean)	Hemoglobin, per Cent (Dare)
1	..	3.88	66
2	..	3.90	68
3	..	3.55	66
4	..	3.15	66
5	..	3.25	55
6	..	3.88	66
7*	1	3.40	54
8	1	4.27	62
9*	3	4.58	66
10*	3	3.60	69
11*	2	3.22	59
12*	1	3.29	57
13*	1	3.59	64
14	1	3.32	55
15*	2	3.68	65
16*	2	4.49	64
17*	1	3.86	62
18	1	3.56	67
19	1	3.40	54
Average for group		3.85	66.67

* Patient died.

(Dare). In the absence of anemia (seventy-nine cases), the average erythrocyte count was 4,200,000 and the average value for hemoglobin was 75 per cent (Dare). In 57 per cent of these cases anemia was definite. In a review of the last forty cases of subacute and chronic glomerulonephritis registered at the Mayo Clinic prior to April 1, 1929, distinct anemia was found in twenty-two (55 per cent) as shown in figure 3. The presence of anemia in glomerulonephritis in the absence of complicating disease or infection is probably evidence of existing or preexisting renal insufficiency and therefore has prognostic value. The absence of anemia in certain cases may be an expression of mild glomerular injury not sufficient to produce renal inadequacy. Further work needs to be done on the clarification of this point.

32. Brown, G. E., and Roth, Grace M.: The Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

Eleven of the twenty-six patients with mixed nephrosis and only three of those with pure nephrosis are dead. Nine of the eleven patients in the first group were anemic, and most of the deaths were the result of uremia. In the second group, one patient died apparently of uremia; one died of unknown cause shortly after arriving home; the third patient also died of an unknown cause. The study of these cases impresses one with the prognostic value of anemia in cases of mixed nephrosis.

The illustrative case reported herein is an example of pure nephrosis without anemia, and it shows clearly the development of anemia coincident with signs of onset of glomerular disease. It is a strong point in favor of the view that severe glomerular involvement and anemia go hand in hand.

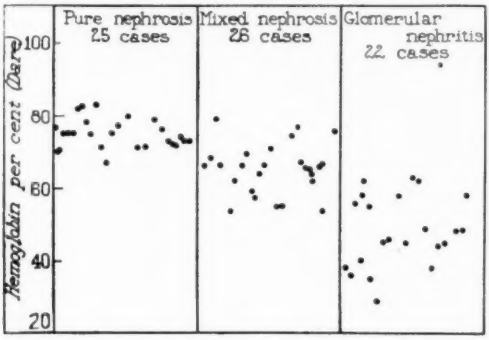

Chart 3.—Incidence of anemia in pure nephrosis, mixed nephrosis and glomerular nephritis.

The studies were made over periods of months to years, and a sufficient number of blood counts was made to give accurate data. In the cases of pure nephrosis, seven of the twenty-five had presented symptoms of the disease for more than five years and yet disclosed blood values that were normal. The fact that the long duration of the disease and therefore its chronicity in some cases show so little effect on the blood count would lead one to believe that the hematopoietic tissues are not affected by the disease process in pure nephrosis.

The results obtained in the present study are not at great variance with those reported in the literature. It was possible to study only two children in the present series, and so the data cannot be compared with those of other workers who have found considerable anemia in children. It would seem logical to believe that nephrosis would affect the blood of children and adults in the same way, and the only explanations for

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the discrepancy in the observations in the reported cases of anemia in children with nephrosis and the absence of anemia in such cases in the present study are: (1) failure of the reported cases to fulfil our criteria for pure nephrosis and therefore the inclusion of mixed cases which may show anemia, and (2) the presence of active infection, that is, of nasal sinus and pneumococcic peritoneal inflammation, in so many of the children with nephrosis.[33]

The studies of the blood volume in pure nephrosis bring out several points: 1. Neither in the stage of edema nor following diuresis is the blood volume increased to a degree to produce dilution phenomena, nor is it decreased to mask anemia, as suggested by Volhard. 2. In mixed nephrosis there may be moderate increase in the volume of plasma and of blood, especially in the presence of anemia, which is probably due to replacement processes incident to diminished erythrocytes and not to edema or diuresis.

In a larger but less rigidly selected group of cases studied by Brown and Rowntree, it was concluded that 50 per cent of cases of nephrosis (pure and mixed) with edema do not show anemia, and in this group strictly normal values for the volume of blood and of plasma are obtained. In the cases that showed slight grades of anemia, the volume of the blood and of plasma was somewhat higher than the mean value for normal persons. In other respects, also, the results recorded here coincide with those of these workers and are therefore reproduced in tabulation form only.

SUMMARY

In only one of twenty-five carefully selected cases of pure nephrosis did the erythrocyte and hemoglobin values show anemia. The leukocyte and differential counts were normal.

In a similar series of twenty-six cases of mixed nephritis of the nephrotic type, the erythrocytes and hemoglobin values showed anemia in nineteen (73 per cent).

In glomerular nephritis and mixed nephrosis, anemia is common, especially in the presence of renal insufficiency; it is of definite prognostic value.

Cases of nephrosis in which signs and symptoms of glomerular nephritis develop show a gradually developing anemia.

The volume of blood in cases of nephrosis, according to corrected body weight, is slightly above the mean value for normal persons.

The presence or absence of anemia in doubtful cases of renal disease with edema is probably of some diagnostic, and of definite prognostic, value.

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33. Davison and Salinger (footnote 19). Clausen (footnote 22).

PULMONARY ATELECTASIS AS A COMPLICATION OF BRONCHIAL ASTHMA*

J. A. CLARKE, JR., M.D.
PHILADELPHIA

Pulmonary atelectasis occurs in two forms, microscopic and macroscopic. The microscopic form has attracted almost no attention so far. It is described in three reports on autopsies in cases of asthma and undoubtedly deserves much more careful study.[1]

The macroscopic form was described early in the nineteenth century. Laennec,[2] discussing a typical case from the practice of Andral,[3] considered it a purely nervous form of asthma. The case is similar in symptomatology and gross pathology to the cases now being recognized as massive collapse.

At about the same time, English surgeons were studying the condition in children as congenital failure of the lung to expand. Following its experimental reproduction by plugging a bronchus in 1845,[4] the condition was forgotten clinically until the works of Pasteur [5] in 1910 to 1914 called attention to its occurrence after operation. This excellent work failed to receive any attention in America until the observations of Scrimger [6] in 1921 and Leopold [7] in 1924, since which time it has been freely discussed by surgeons and roentgenologists. Atelectasis was also used by Jackson, Spencer and Manges [8] since 1920 as an aid in the localization of nonopaque foreign bodies in the lungs.

Atelectasis occurs either as a result of pressure on a normal lung, as in hydrothorax and pneumothorax, or as a result of obstruction of a bronchus by tumors or foreign bodies. It can be produced experimentally by obstructing a bronchus. Its occurrence as a postoperative compli-

* Submitted for publication, Sept. 4, 1929.

* From the Asthma Clinic of Jefferson Hospital.

* Read before the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 5, 1929.

1. Huber, H. L., and Koessler, K. K.: Pathology of Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922. Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma: Report of Three Cases, Arch. Path. **5**:1003 (June) 1928. Steinberg, B., and Fegley, K. D.: J. Lab. & Clin. Med. **13**:921, 1928.

2. Laennec: Traite de l'auscultation mediate, ed. 2, Paris, 1826, vol. 2, p. 87.

3. Andral: Clinique Médicale, ed. 2, Paris, 1829, vol. 1, p. 250.

4. Mendelssohn, A.: Der Mechanism der Respiration und Cirkulation, Berlin, B. Behrs, 1845, p. 177.

5. Pasteur: Lancet **2**:1080, 1910.

6. Scrimger: Surg. Gynec. Obst. **32**:486, 1921.

7. Leopold: Am. J. M. Sc. **167**:421, 1924.

8. Jackson, Spencer and Manges: Am. J. Roentgenol. **7**:277, 1920.

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cation was proved, in a large number of cases, to be due to a plug of tenacious mucus in a large bronchus.

In typical bronchial asthma the occurrence of massive collapse was reported three times, once by Berkhard [9] in 1889, once by Kamchorn and Ellis [10] in 1921 and once by Sante [11] in 1928. In Andral and Laennec's case the symptoms, signs and observations at autopsy point strongly to atelectasis. The man had had a chronic cough for years, but had not had dyspnea until a few hours before death. Laennec, however, considered the attack asthma.

The case of Berkhard and that of Kamchorn and Ellis undoubtedly occurred in persons who had been asthmatic for many years. Both, however, were complicated by cardiac failure. These observers believed that their patients died in asthmatic paroxysms.

There are few notes on Sante's case, but there can be no doubt but that the child had asthma. This case was complicated by the presence of pneumothorax on the same side as the atelectasis, but the atelectasis was not caused by the pneumothorax. After examining the roentgenograms of Sante, one is easily convinced of the accuracy of his interpretation, paradoxic as it may seem at first. The child made a complete recovery from both conditions. There was no previous operative work in any of the three cases.

In addition to these three cases, two additional cases are here reported; in one the condition was diagnosed by routine roentgen examination and in the other at autopsy. Both patients showed the same symptoms as in the postoperative cases. One patient recovered completely, as is shown by the roentgenograms.

REPORT OF CASES

CASE 1.—J. W., a white woman, aged 32, married, came to the asthma clinic on July 12, 1928. Her paternal grandfather had had asthma after he was 80. Soon after an attack of "typhoid-pneumonia" at 5 years of age, she developed asthma, which continued at intervals, becoming worse during the last few years before examination.

Physical examination showed an emaciated young woman with a large, flat chest. The wheezing râles of asthma were heard all over both lungs. The heart showed a split first sound and a systolic murmur at the apex. Roentgen examination showed adhesions of the right diaphragm. The heart was small and normally placed, and both lower lobes were normally distended with air. The nasal septum was deflected, but no definite disease of the accessory sinuses was diagnosed by either rhinologist or roentgenologist. The teeth were in poor condition, and four abscesses were found at their roots. There were no positive skin reactions.

9. Berkhard: Asthma, ed. 2, London, 1889, p. 73.

10. Kamchorn and Ellis: Am. J. M. Sc. **161**:525, 1921.

11. Sante: Am. J. Roentgenol. **20**:213, 1928.

On July 27, she was seized with such a severe paroxysm of dyspnea that her private physician, Dr. Bender, thought she was dying. She was admitted to the ward on the following day. Another roentgenogram was taken on August 1 and showed the right lower lobe collapsed, with the heart and trachea displaced to the right side. A third picture, taken on August 9, showed the lung still collapsed, but the displacement of the heart was not so great. On August 10, bronchoscopy was done by Dr. Clerf, but no obstruction was found.

A final picture, taken on September 13, showed the previously collapsed lobe completely expanded.

She had an irregular fever (the highest temperature recorded being 102.6 F.) for the first four days of her stay in the hospital. The highest respiratory rate

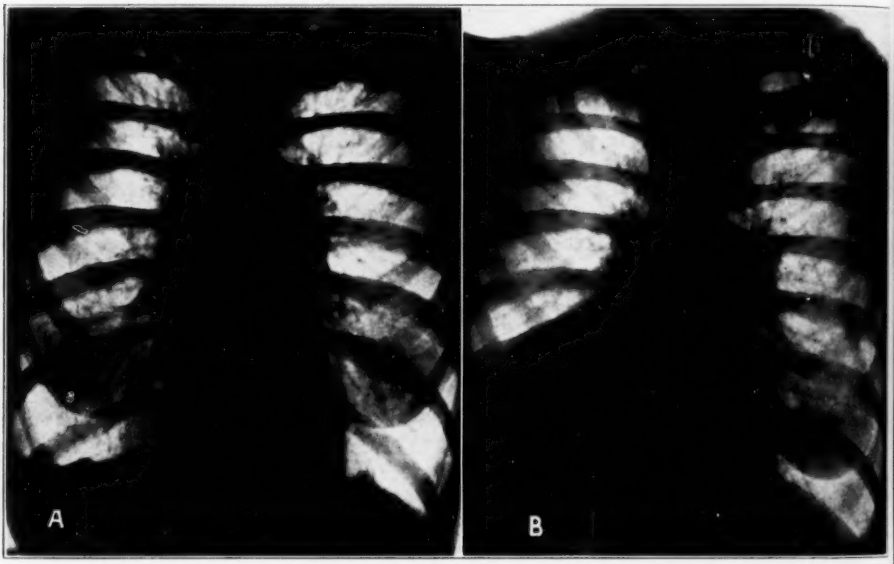

Fig. 1 (case 1).—*A*, lungs two weeks before atelectasis, showing diaphragmatic adhesions and expansion of right lower lobe; *B*, three days after onset of atelectasis.

was 36 per minute. The asthma decreased in severity rapidly, but was never completely relieved.

Case 2.—M. K., a white woman, aged 53, unmarried, was admitted to the ward on July 25, 1928. She had asthma for twelve years previous to admission, but was able to work as a domestic servant for most of that time. The asthma was worse following "congestion of the lungs" two years before admission. At the time of admission, she was continuously in a dyspneic condition, except when relieved by doses of epinephrine.

Physical examination showed typical wheezing râles of asthma. A roentgenogram taken on July 28 showed a marked increase in the root shadows and the peribronchial markings. There was air in both lower lobes. The laboratory reported a faint trace of albumin with a few granular casts in the urine. The temperature did not rise above 99.5 F. There were positive skin reactions to grass

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pollen, orris root, horse and cat dander. Examination of the nasal sinuses showed no disease. The teeth had all been removed.

On August 1, at 12:30 a. m., the patient said that she was weak and had a headache. Since she had had eight doses of epinephrine during the previous twenty-four hours, she was given ¼ grain (0.016 Gm.) of morphine, after which she slept. At 5:15 a. m., it was noticed that she was dyspneic and cyanotic and was unconscious. The heart was beating regularly 120 beats per minute. She was given artificial respiration with 10 per cent carbon dioxide and oxygen, strychnine, atropine, alpha lobeline, caffeine and epinephrine. She became weaker, and died at 6 p. m. without regaining consciousness.

Necropsy was performed by Dr. Bucher. The pericardial space was prominent. The thymus extended to the upper border of the heart; the right side of

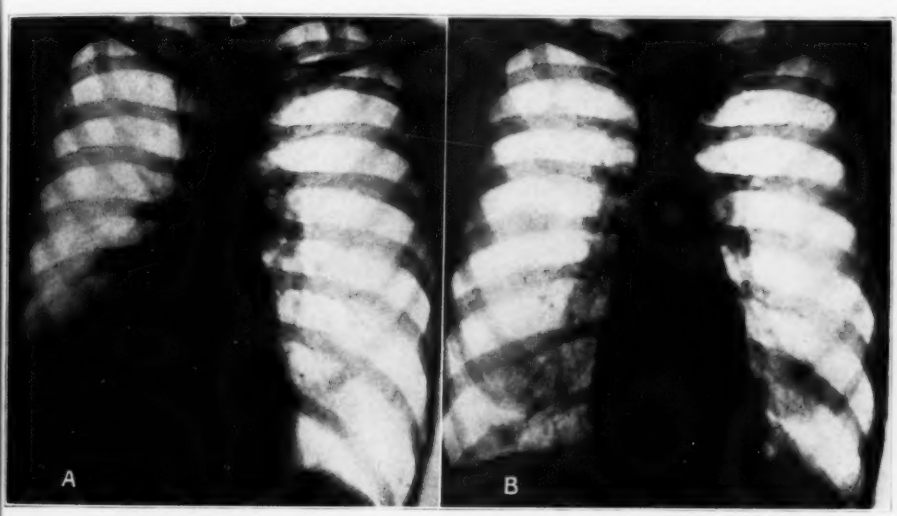

Fig. 2 (case 1).—*A*, lungs eleven days after onset of atelectasis; *B*, six weeks after onset of atelectasis, showing return to normal.

the heart was dilated. The upper lobes of the lungs were voluminous; the lower lobes were flabby and airless.

The tracheal mucous membrane was red and swollen, and the smaller bronchi were filled with yellowish, tenacious mucus. There was a mass of lymph nodes at the junction of the trachea with the left main bronchus. There were many distended air vesicles on the surface of the lungs.

On section, the upper lobes were emphysematous and the lower lobes were red and soggy. On histologic examination, focal atelectasis and bronchial obstruction by mucus were found.

The heart weighed 330 Gm. and had two papillary muscles. The myocardium was grayish red and somewhat flabby. There were a few petechial hemorrhages on the epicardium. Considerable thymic tissue was found in the fibrotic thymus. The liver was normal. The spleen was small but contained a number of small

miliary, grayish-white, calcified nodules. The kidneys and gastro-intestinal tract were normal. There were a few myomas in the small uterus.

A careful study of the reported cases of postoperative atelectasis reveals a percentage of allergic manifestations far higher than that of the general population. Scott [12] reported forty cases in 1925, four of his own and thirty-six from the literature. In spite of the fact that no family histories were given and that the past medical histories were meager, one finds that in five patients there were unmistakable manifestations of allergy before operation. Three patients had had

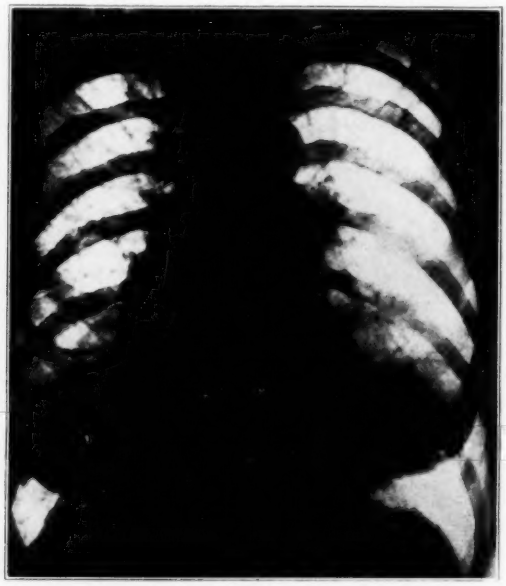

Fig. 3 (case 2).—Lungs four days before atelectasis and death, showing normal aeration of both lower lobes.

asthma and one urticaria, and one had been operated on for angioneurotic edema of the intestines. Two other patients had had an undiagnosed chronic cough. One had an acute edema of the glottis of the "angioneurotic type" after the operation. Bowen [13] reported seven cases, in one of which the patient had been asthmatic before operation.

12. Scott, W. J. M.: Postoperative Massive Collapse of Lung, Arch. Surg. **10**:73 (Jan.) 1925.

13. Bowen: Am. J. Roentgenol. **21**:101, 1929.

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Thus one sees that without the observers' attention being especially directed to allergy, they reported frank allergic manifestations in more than 10 per cent of the cases.

The occurrence of râles in both lungs before the onset of atelectatic symptoms was frequently noted. Elliott and Dingley [14] insisted that bronchitis always preceded the collapse. Ball [15] considered and discarded the theory of the asthmatic nature of the condition, because atelectasis is not a complication of asthma.

Because of the high incidence of allergy in persons with postoperative atelectasis, and the occurrence of atelectasis in persons with asthma on whom surgical procedures have not been carried out, it is suggested that there is an allergic factor in postoperative atelectasis. This may be the bronchitis which is responsible for the tenacious mucus which, in turn, was shown to produce the obstruction in many instances.

Clinically, surgeons recognize two types of atelectasis. In the fulminating type, the onset is sudden, with extreme dyspnea, sense of oppression and cyanosis, and in patients with the more severe cases, with coma and death. As Lee aptly put it: "The patient suddenly presents symptoms of a catastrophe." All of the five patients suffering from asthma exhibited these symptoms. In this type, the symptoms are not explained by either the necropsy or the roentgen observations. The other type is spoken of as a latent type. Here the symptoms are only those of mild respiratory infection, and the dyspnea is only that which is to be expected when a certain amount of lung tissue fails to function.

The explanation of the difference in the two types by the time required to produce the collapse is untenable, because it was shown experimentally that partial obstruction produces obstructive emphysema, and that collapse cannot start until the obstruction is complete. The rate of absorption of the captured air by the blood is probably determined by chemical laws and is not subject to variations.

The suggestion is made here that the fulminating symptomatology of atelectasis is an allergic reaction to the bronchial secretion captured in the collapsed lung and absorbed along with the air, similar to that which one is accustomed to call bronchial asthma. The absence of the typical asthmatic râles over the noncollapsed lobes of the lungs is one point distinguishing this from the ordinary less severe paroxysms of asthma.

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14. Elliott and Dingley: Lancet **1**:1305, 1914.

15. Ball, R. P.: Pulmonary Atelectasis Following Thyroidectomy: Report of Four Cases with Observations at Necropsy, Arch. Path. **5**:763 (May) 1928; Bilateral Lobar Atelectasis: Report of Case with Autopsy Observations, Arch. Surg. **17**:82 (July) 1928.

Small areas of collapsed alveoli were found at necropsy a number of times in persons who had asthma. It seems possible that lobar collapse might result from the coalescing of a number of such areas until the whole lobe would be involved without any obstruction in the larger bronchi. Ball was unable to find any obstruction in the bronchi in four patients, all of whom had lobar collapse.

In the course of asthma, the occurrence of small areas of collapse giving rise to severe paroxysms of dyspnea, which, however, do not prove fatal, is probably fairly frequent. Suggestive roentgen shadows appear and disappear, and on physical examination of the patient scattered areas of diminished breath sounds and moist râles make their appearance from time to time. Acute obstructive emphysema should not be forgotten when such areas are found.

SUMMARY

Lobar atelectasis of the lungs (massive collapse) occurs in persons with bronchial asthma independent of operative procedure and is frequently fatal.

In postoperative atelectasis, previous symptoms of allergy are not uncommon.

The fulminating symptoms are suggestive of an allergic reaction to the captured bronchial secretion.

Small areas of pulmonary atelectasis are probably not uncommon in persons with true bronchial asthma and may explain some of the severe paroxysms.

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TETRALOGY OF FALLOT

CLINICAL REPORT OF A CASE *

L. MINOR BLACKFORD, M.D.

ATLANTA, GA.

White and Sprague [1] have recently reproduced extracts from Fallot's original monograph (1888), some of which may be appropriately repeated:

> Of these cardiac malformations there is one which in frequency surpasses all others, since we have noted it in almost 74 per cent of our observations. It is this malformation, then, that the clinician will be justified in diagnosing, and in so doing the chances of error which he will run will be relatively few.
>
> This malformation constitutes a true pathologic-anatomic type represented by the following tetralogy: (1) stenosis of the pulmonary artery [he might have added "or of the pulmonary valve or infundibulum"], (2) interventricular septal defect, (3) deviation of the origin of the aorta to the right and (4) hypertrophy of the right ventricle, almost always concentric in type. At times there is an additional entirely accessory defect; namely, patency of the foramen ovale.
>
> One cannot at the present time attribute the maladie bleue to the persistence of the foramen ovale without direct opposition to the great majority of observed facts; when the communication between the two auricles exists alone without any other associated cardiac lesion, cyanosis does not result.

This combination of lesions is ascribed by Abbott,[2] largely on the basis of studies by Sir Arthur Keith, to an arrest of development before the eighth week of embryonic life.

Kurtz, Sprague and White [3] have reported three cases of the tetralogy of Fallot with necropsy, in two of which the condition was

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* Submitted for publication, Aug. 5, 1929.

* From the Emory University Division, Grady Hospital.

* For this article the author was awarded the Luther C. Fischer prize for the best written paper presented before the Fulton County Medical Society by a member in 1929.

* The patient was presented before the Fulton County Medical Society, July 18, 1929.

1. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot: Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, J. A. M. A. **92**:787 (March 9) 1929.

2. Abbott, M. E.: Congenital Cardiac Disease, in Osler and McRae: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 613.

3. Kurtz, C. M.; Sprague, H. B., and White, P. D.: Congenital Heart Disease: Interventricular Septal Defects with Associated Anomalies in a Series of Three Cases Examined Postmortem, and a Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of the Fingers, Am. Heart J. **3**:77 (Oct.) 1927. The tetralogy of Fallot was found in two of the necropsies reported in this paper and more recently at necropsy (see footnote 1) in the clinical case.

diagnosed during life; the ages of these patients were 23, 11 (no pulmonic valves) and 59. Cahan,[4] in a study of 10,333 school children, found 94 cases of heart disease, 10 of which were congenital in origin; in 1 of these, the condition was diagnosed patent interventricular septum with pulmonic stenosis. Mainzer [5] has reported a clinical case in a man, aged 25, with 18.87 Gm. of hemoglobin per hundred cubic centimeters and 7,600,000 red blood cells. I have not been able to find any other records with or without necropsy since the recent comprehensive summary of the literature by Abbott.[6] Her original work in the field of congenital cardiac disease and careful reviews not only have illuminated its pathogenesis and pathology, but have facilitated its diagnosis, exactitude in which is of prognostic importance. For purposes of clinical classi-

*Abbott's Clinical Classification of the Markedly Cyanotic Group (from Blumer's Bedside Diagnosis)**

Lesions	Maximum Age in Years	Number of Cases	Average Age in Years
Dextroposition of aorta with localized interventricular septal defect but no pulmonary stenosis ("Eisenmenger complex")	33	8	16
Pulmonary stenosis with interventricular septal defect and dextroposition of aorta (Tetralogy of Fallot)	36	73	11
Cor biloculare with transposition of great trunks	17	2	9
Pulmonary atresia with defect of interventricular septum and patent ductus	13	24	3
Transposition of arterial trunks with interventricular septal defect and patent ductus	16	15	2½
Persistent truncus arteriosus (complete defect of aortic septum) with localized defect of interventricular septum	12	24	2

* Order based on degrees of oxygen-unsaturation and duration of life in recorded cases with autopsy.

fication, she has tabulated according to their pathologic bases the conditions that result in marked cyanosis. It is this group only that need be considered here.

Patients with marked cyanosis are sometimes highly intelligent,[1] but more often they are stunted mentally as well as physically. In cases of long-continued cyanosis there is an adaptation of the cells of the body to a subnormal supply of oxygen. The low oxygen tension apparently leads to an accumulation of toxic metabolites in the body tissues of

4. Cahan, J. M.: The Incidence of Heart Disease in School Children, J. A. M. A. **92**:1576 (May 11) 1929.

5. Mainzer, Fritz: Analyse eines kongenitalen Herzfehlers (zugleich ein Beitrag zur Bedeutung der Haemoglobinvermehrung bei Sauerstoffmangel), Ztschr. f. klin. Med. **108**:489, 1928.

6. Abbott, M. E.: The Diagnosis of Congenital Cardiac Disease, Part II, True "Morbus Caeruleus," in Blumer, Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, vol. 2, p. 430; Ventricular Septal Defects, ibid., p. 420. These monographs of Dr. Abbott's have provided most of the introductory material in this paper.

Fig. 1.—Fundus oculi: duskiness, neuroretinitis and increase in number of vessels.

those regions in which the circulation is poorest. There is also an increase in the number of patent capillaries with dilatation of their lumina, which may be seen in the retina, associated at times with neuroretinitis. This accumulation of waste products and the increase in capillary volume seem to be the chief causes of clubbing of fingers and toes.

There is also compensatory increase in the number of red blood cells. In cases of pronounced polycythemia, orthostatic albuminuria may occur, as well as epistaxis, hemoptysis and even hematemesis. Vaquez and Bordet (Abbott) stated the belief that the presence of more than

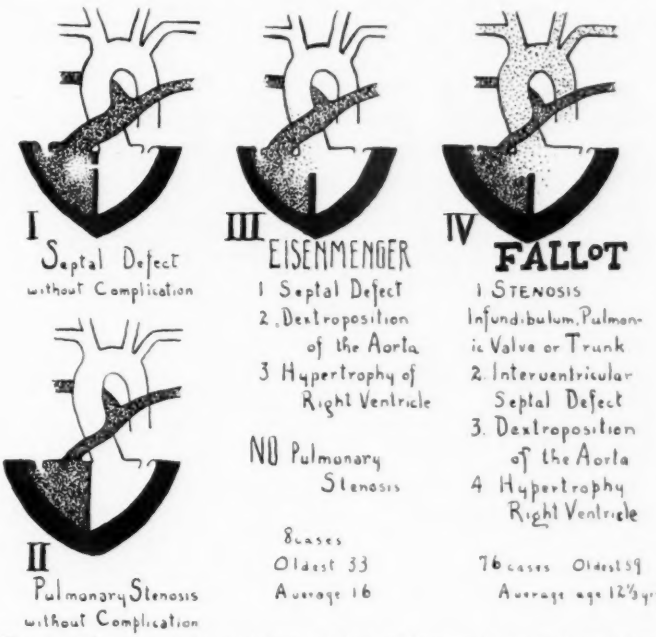

Fig. 2.—Diagram of the pathology of the tetralogy and of allied conditions.

6,000,000 erythrocytes is a grave omen. However, Wintrobe and Miller [7] found in a study of 100 healthy medical students, aged 19 to 30, that the number of erythrocytes averaged 5,850,000, with two counts (7,350,000 and 7,530,000) above 7,000,000. The hemoglobin in this series ranged from 13.4 to 18.3 Gm. per hundred cubic centimeters of blood, averaging 15.87 Gm.

As Fallot observed, uncomplicated patent foramen ovale does not cause cyanosis. Interventricular septal defect alone is often of little

7. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929.

clinical significance, and does not cause cyanosis without failure of the left ventricle. Pulmonary stenosis with intact interventricular septum may not cause cyanosis or other symptoms for the first ten or fifteen years of life. A slightly patent ductus arteriosus rarely causes symptoms or cyanosis, and a widely patent one is associated with other anomalies incompatible with life beyond early infancy. In brief, marked cyanosis of long duration in the case of an adult is almost certainly due either to the tetralogy of Fallot, or to the "Eisenmenger complex," which is the same thing except that there is no pulmonic stenosis.

Cases of the tetralogy, in addition to the invariable deep cyanosis and clubbing from earliest infancy, often present a thrill and harsh systolic murmur just to the left of the sternum. These are usually maximal in the second interspace; it has been maintained that when the murmur is loudest below this that the stenosis is infundibular rather than pulmonic, but exception has been taken to this view.[8] The murmur is usually well transmitted to the vessels of the neck. In the majority of instances the area of cardiac dulness is markedly increased above and to the right, but in some, in spite of great hypertrophy of the right ventricle, this is not made out, owing to the rotation of the heart on its vertical axis. Enlargement of the right ventricle and often increased breadth of the ascending aorta may be seen in the roentgenogram. The electrocardiogram shows right ventricular preponderance and increased amplitude of the P-waves and sometimes of the T-waves as well. The differential diagnosis, then, is virtually a question of the size of the pulmonary outlet. When there is no stenosis at this orifice, cyanosis may not develop until late, thrills are absent, murmurs are not transmitted above the base of the heart, and roentgen examination reveals hypertrophy of the conus pulmonalis. A typical case of the "Eisenmenger complex" has recently been communicated by Baumgartner and Abbott.[9]

It has been shown[10] that in one type of cardiovascular anomaly syphilis is not more common than in the general population; it is not therefore an etiologic factor in that condition. It has not been established that syphilis is common in cases of tetralogy of Fallot.

There is no specific treatment for the tetralogy of Fallot. Every person afflicted with congenital heart disease should live within his physical limitations and, on account of the frequency of death from sub-

8. Raab, W.; Weiss, R.; Lowbeer, B., and Rihl, J.: Untersuchungen über einen Fall von kongenitalen Herzvitium, Wien. Arch. f. inn. Med. **7**:367, 1924.

9. Baumgartner, E. A., and Abbott, M. E.: Interventricular Septal Defect with Dextroposition of Aorta and Dilatation of the Pulmonary Artery ("Eisenmenger Complex"), Terminating by Cerebral Abscess, Am. J. M. Sc. **177**:639 (May) 1929.

acute bacterial endocarditis in such cases, should have all possible foci of infection removed, as has long been advocated by many authors, including myself.[10]

White and Mudd[11] have reported eight cases of angina pectoris in persons less than 30, associated in each case with aortic regurgitation of rheumatic origin, and have assembled thirty-four similar ones. In none was a diagnosis of congenital defect made. Willius,[12] it is true, has seen extensive coronary disease at necropsy in three cases of persons less than 30. In two other communications with associates in the

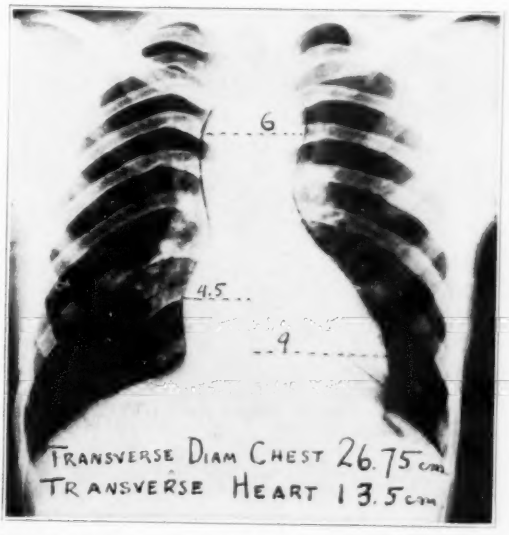

Fig. 3.—Roentgenologic appearance of heart at 7 foot tube distance. Heart shadow is round and is increased transversely owing to right ventricular enlargement. In the region of the conus pulmonalis the shadow is concave and does not show the prominence often seen in cases of patent ductus arteriosus, and always seen in cases of the Eisenmenger complex.

Mayo Clinic,[13] Willius has expressed the opinion that cardiac pain is essentially due to "coronary circulation insufficient either in amount or

10. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

11. White, P. D., and Mudd, S. G.: Angina Pectoris in Young People, Am. Heart J. **3**:1 (Oct.) 1927.

12. Willius, F. A.: The Protean Manifestations of Disease of the Coronary Arteries, New Orleans M. & S. J. **80**:143, 1927.

13. Barnes, A. R., and Willius, F. A.: Cardiac Pain in Paroxysmal Tachycardia, Am. Heart J. **2**:490 (Dec.) 1927. Willius, F. A., and Giffin, H. Z.: The Anginal Syndrome in Pernicious Anemia, Am. J. M. Sc. **174**:30 (July) 1927.

in oxygen saturation." Keefer and Resnick [14] have recently reviewed the whole subject of angina and have concluded that it is always due to anoxemia of the myocardium. This syndrome is rare in congenital cardiac disease.

REPORT OF CASE

History.—An illiterate negro, aged about 20, reported to the dispensary of Grady Hospital on May 10, 1929, complaining of pain over his heart. His father had died of pneumonia; his mother, four brothers and four sisters were living and

Fig. 4.—The patient.

well. He was ill with influenza during the World War, but had never been confined to bed at any other time. When he was a boy, he could run short distances as fast as his playmates, but he could never run as far on account of shortness of breath. This shortness of breath had interfered with his activities as long as he could remember, and he had never been as stout as his brothers and sisters. His nails had always been curved. He freely admitted sexual promiscuity and excesses, but had the usual ingenious, if apocryphal, explanation of a phallic lesion. The Wassermann reaction was negative at the Grady Hospital in 1928.

14. Keefer, C. S., and Resnick, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928.

When the patient was about 14 years old he secured employment in a sawmill. Unusual exertion in the mill would bring on sharp, stabbing pain, beginning near the apex of the heart and radiating up to the base. These pains were severe, but a few moments of rest would relieve them. On one occasion his shoulder was supporting one end of "a great big log" and something slipped and he had to support the log alone a few seconds; just after this he felt the most awful stabbing pain in his heart that he had ever felt, and he spit up a little blood. He had had some bleeding from the nose and had coughed up blood from time to time since, and he had observed that his sputum was always brown. About three years previous to admission he came to Atlanta to live. That year his ankles began to swell toward evening, but he had not noticed this recently. He had suffered a great deal from generalized headache, but subjective pounding of the heart had been rare. He had been working as janitor in a small apartment house for about two years. Ordinary exertion, including shoveling coal, had not bothered him much, but heavy lifting had always brought on cardiac pain. Late in April of this year

Fig. 5.—Clubbing of fingers and toes.

he carried a heavy box upstairs and was seized with agonizing pain, second only to that experienced once in the sawmill. Unlike the former seizures, this one lasted for some time, and similar attacks began to come on without undue exertion several times a day. It was on account of the frequency, severity and duration of these that he came to the clinic.

Examination.—The patient was 62½ inches (159 cm.) tall and weighed 104 pounds (47.2 Kg.). His state of nutrition and muscular development was only fairly good. The skin of the trunk was dark, but that of the head and extremities, particularly of the lips, ear lobes, fingers and toes, was almost blue-black. The interpalpebral sclerae were purplish-brown; on pulling down the lids numerous blue vessels coursing over pale blue sclerae were exposed. The inner aspects of the lips were purplish slate. Pigmentation of the mucous membranes of colored persons, particularly of the highly pigmented ones, is not unusual, but pressure on the lip in this instance drove out the purplish hue, thus proving that the color was due to profound cyanosis. The tongue was also cyanotic. Clubbing of the fingers and

toes was extreme. The teeth were in good condition. The tonsils were moderately enlarged and cryptic; the anterior cervical glands were also enlarged. The thyroid gland was of normal size and the lungs were clear. Just to the left of the sternum a "distant" thrill was palpable in the second, third and fourth interspaces, most pronounced in the fourth. Cardiac dulness extended 3 cm. from the midline in the third left interspace, 2 cm. in the fourth right interspace and 8 cm. in the fifth left interspace. A prolonged, harsh systolic murmur was heard all over the precordium, indeed all over the chest, but it was loudest in the fourth interspace at the left

Fig. 6.—Electrocardiogram showing right ventricular preponderance and increased amplitude of the P and T waves in Leads I and II. (Courtesy of Dr. L. M. Bonner.)

border of the sternum; in the back the maximal intensity of the murmur was in the left interscapular space. There was no diastolic murmur. On palpation the prostate seemed normal. There was no evidence of edema of the extremities, and the tendon reflexes were normal. The retina was dusky, especially around the nerve-head for a radius of about three disk-diameters. The arterioles were about the color of normal retinal veins, and the veins were much darker and appeared somewhat dilated; both appeared to be increased in number. Moderate neuroretinitis was evidenced by 1 diopter of papilledema.

The blood pressure was 110 systolic and 60 diastolic (mercury manometer). During the period of observation in the hospital the pulse was usually about 60. The venous blood contained 19.4 Gm. of hemoglobin per hundred cubic centimeters (Newcomer standard), 125 per cent according to the average normal of Wintrobe and Miller. The laboratory of biochemistry reported the hemoglobin of capillary blood to be 18.5 Gm. The erythrocyte counts of the venous blood were 7,660,000 and 7,760,000 and averaged 7,710,000. The leukocytes numbered 5,950, and the differential count was normal. The first specimen of urine, voided when the patient was ambulatory, gave albumin, grade 3, no casts, 5 to 8 red cells per high power field and a few pus cells. After rest in bed albumin was graded 1, and an occasional granular cast was reported, but no red cells. The phthalein output was 60 per cent in two hours. The icterus index was 15, nonprotein nitrogen 35, creatinine 1.5 and blood sugar 101. The Wassermann reaction was strongly positive.

Dr. Lila M. Bonner said of the electrocardiogram: "There is right ventricular preponderance. The P and T waves in Leads I and II are sharp and prominent."

Dr. J. J. Clark reported concerning the teleoroentgenogram of the heart: "The transverse diameter of the inside of the thorax is 26.75 cm. The right border of the heart is 4.5 cm. from the midline, the left border 9 cm. The ascending aorta is 6 cm. wide."

Course.—After a week's rest in the hospital, the patient felt better and was released. A few weeks later, tonsillectomy was done under local anesthesia. He is now receiving mild antisyphilitic treatment and leading an inactive life. The Family Welfare Society is trying to find him suitable work; this is difficult on account of his total lack of education and training.

COMMENT

It is true that in some cases of the tetralogy of Fallot the increased width of the ascending aorta is more prominent than in this, and yet the roentgenogram in this case is strikingly like that in the case of White and Sprague. Moreover the descriptions of the physical examinations are remarkably similar; it is most improbable therefore that there is a difference in the pathologic bases of the two. In my case, however, the maximal murmur is in the fourth interspace. This may indicate that the stenosis is below the pulmonic valve, that is, that it involves the infundibulum.

As already pointed out, in cases of marked cyanosis of long standing in an adult, the diagnosis of septal defect with dextroposition of the aorta is all but certain; the differential point is the presence or absence of stenosis in the pulmonary system. In this case physical signs and the roentgenogram prove that one is not dealing with the "Eisenmenger complex." I believe therefore that in making the diagnosis of the tetralogy of Fallot the chances of error that I run are relatively few. I present this report then without waiting for necropsy, partly because Kurtz, Sprague and White first so presented theirs and also because the indigent negroes are hard to keep track of, and the prospects for ultimate necropsy in this case are accordingly not too good.

It is interesting to speculate as to the cause of the cardiac pain. At first it would seem to be syphilitic in origin. However, this patient has been suffering from this type of pain for five years or longer and, in spite of his sexual precocity, it is not probable that he had contracted syphilis at such an early age that it would be far enough advanced to cause these symptoms at 14. His numerous healthy brothers and sisters and their children constitute an argument against congenital syphilis and, finally, the negative Wassermann reaction in 1928 would indicate that he contracted syphilis but recently. It is evident that the oxygen supply to the whole body is poor; therefore I believe that this pain which comes on following exertion is due to anoxemia of the myocardium, that is, is true angina, and that this anoxemia is the direct result of the dextroposition of the aorta.

The retinal picture is striking. The increase in hemoglobin and erythrocytes is characteristic. Orthostatic albuminuria is well illustrated, as well as hemoptysis and epistaxis.

SUMMARY

A clinical case of the tetralogy of Fallot associated with angina pectoris is reported.

NOTE: Dr. R. S. Leadingham told me at the meeting of the Fulton County Society that he had recently made the diagnosis of the tetralogy of Fallot on his service at the Georgia Baptist Hospital, and has showed me his patient. Although the thorax in his case is smaller than in mine, the outlines of the hearts in the teleoroentgenograms can be almost exactly superimposed; the relative hypertrophy in his case is therefore greater than in mine and the prognosis accordingly graver. Dr. Leadingham is reporting his case elsewhere: necropsy was performed in December, 1929.

SPASM-PRODUCING SUBSTANCE IN THE SPUTUM OF PATIENTS WITH BRONCHIAL ASTHMA*

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In 1922, Zeydner and van Leeuwen [1] reported the presence of an alcohol-soluble, toxic substance in the blood of twelve persons suffering from asthma, urticaria and migraine which had a definite stimulating action on smooth intestinal muscle. The method of extraction of this substance, that of Freund,[2] was designed to eliminate those normal stimulating and augmentor substances which may appear in any serum during the process of clotting. When safeguarded in such a manner, this technic yielded negative results with the blood serum of normal controls, whereas a definite action was demonstrable with the serum of persons with an "allergic disposition."

The many difficulties encountered in the utilization of blood extracts with Freund's method have been emphasized by Clark and Gross,[3] who showed that the substance present in normal serum has a strong stimulant action on the isolated uterus and an irregular action on the isolated intestine of the rat. This substance is also alcohol-soluble and dialyzable and therefore cannot easily be eliminated. In view of their observations, it was determined to investigate the sputum instead of the blood of the patients with bronchial asthma for spasm-producing substances. In this investigation sixteen cases of bronchial asthma and forty-three controls were employed.

EXPERIMENTAL WORK

Sputum from asthmatic patients was collected in 6 ounce bottles containing 95 per cent alcohol. Separate specimens were collected before, during and after an attack of asthma. The sputum was allowed to stand overnight, and on the following day it was shaken and filtered through coarse filter paper. The alcohol filtrate was then evaporated at a temperature not exceeding 56 F., and the residue which had a yellowish resinous appearance was dissolved in 10 cc. of Tyrode's solution.

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* From the Laboratories of the Mount Sinai Hospital.

1. Zeydner and van Leeuwen, W. Storm: Occurrence of a Toxic Substance in the Blood in Cases of Bronchial Asthma, Urticaria, Epilepsy and Migraine, Brit. J. Exper. Path. **3**:6 (Dec.) 1922.

2. Freund, H.: Arch. f. exper. Path. u. Pharmakol., vol. 91, p. 272.

3. Clark, A. J., and Gross, L.: The Action of Blood on Isolated Tissues, Arch. internat. de pharmacod. **28**:243, 1923-1924.

This sputum extract was tested for spasm-producing properties on isolated intestines of cats and of rabbits which had been prepared as follows: A segment of the jejunum from a cat was opened, the mucosa was stripped, and a piece of muscle one-half inch in length was suspended in a bath of Tyrode's solution at 37 C. which was supplied with a constant stream of oxygen. The muscle was attached to a lever which recorded its contractions on a slowly revolving drum. Whenever a rabbit's intestine was employed, about three fourths of an inch of the intact gut obtained from the duodenum or from the jejunum was used. Frequently before and after each experiment the relative contractility of the gut was ascertained by testing its response to 0.005 mg. of pilocarpine.

TABLE 1.—*The Effect on Cats' Intestine of Alcohol-Soluble Extracts from Sensitive Asthmatic Patients*

Patient	Sensitive to	Spasmophilic Reaction of Sputum
1—D.	Chicken feathers	Positive
2—Deg.	Goose feathers	Positive
3—M. v. D. B.	Oat infested with mites	Positive
4—F.	Dust	Positive
5—B. W.	Dust	Positive
6—B.	Horse dander and dust	Positive
7—B.	Horse dander	Positive
8—O.	Horse dander	Positive

TABLE 2.—*The Effect on Rabbits' Intestine of Alcohol-Soluble Extracts from Sensitive Asthmatic Patients*

Patient	Sensitive to	Spasmophilic Reaction of Sputum
9—A. C.	Ragweed, goose feathers, timothy	Positive
10—C. S.	Cottonseed, chicken and pigeon feathers	Positive
11—R.	Rabbit hair, sheep wool	Positive
12—G.	Timothy	Positive
13—C. P.	Timothy and ragweed	Positive
14—F.	Plantain, timothy and ragweed	Positive
15—D.	Horse dander, dog hair, timothy, sheep wool	Positive
16—D.	Plantain and Hudson seal	Positive

When it was definitely established that the muscle strip was functioning properly, from 1 to 2 cc. of the sputum extract was introduced into the bath, and the results were recorded on the revolving drum. In the first two of the earliest cases the unextracted sputum was obtained during the patient's attack. The muscular contraction produced by this sample which was diluted in 10 cc. of Tyrode's solution was prompt and sustained. In order to exclude the presence of derivatives of split proteins brought about by the action of bacteria on the proteins in the bronchial secretions, which might be responsible for a stimulating action on the suspended muscle, only alcohol-extracted sputum was used in subsequent experiments.

The first series of experiments was performed on cats' and the second on rabbits' intestines. The latter, as seen in the illustrations, is not so suitable for this work as the former. This is evidenced by the weaker contraction of the rabbits' strip

as compared with the cats'. A definite contraction of the segment after the introduction of the intestinal strip indicated a negative reaction.

RESULTS

The alcohol-soluble extracts from sixteen allergic, asthmatic patients invariably produced spasm of both rabbits' and cats' intestine in vitro (tables 1 and 2). Variations in the degree and promptness of the reaction occurred following the use of sputum extract from different cases. This is best shown in the illustrations.

TABLE 3.—*Effect on Rabbits' and Cats' Intestines of Alcohol-Soluble Extracts from Nonsensitive Asthmatic Patients*

Patient	Diagnosis	Spasmophilic Reaction of Sputum
R.	Pansinusitis	Negative
Br.	Suppurative ethmoiditis	Negative
R.	Bilateral suppurative ethmoiditis	Negative
F.	Chronic bronchitis and tuberculosis	Negative
K.	Pansinusitis	Negative

TABLE 4.—*Control Cases*

Diagnosis	Number of Cases	Reaction
Tuberculosis	8	Negative
Bronchiectasis	4	Negative
Bronchitis	1	Negative
Pulmonary neoplasm	1	Negative
Valvular disease	6	Negative
Healthy subjects	5	Negative
Resolving pneumonia	4	Negative
Sinus infection	1	Negative
Grip	1	Negative
Colitis	1	Negative
Abscess of lung	6	Negative
Acute lobar and bronchopneumonia	5	Positive

The sputum of five nonsensitive, asthmatic patients did not contain a smooth, muscle-stimulating substance (table 3).

Thirty-eight control subjects gave no evidence of any spasmophilic substance comparable to that found in the sputum of allergic asthmatic patients (table 4).

The sputums of five patients with acute lobar pneumonia and bronchopneumonia contained a smooth, muscle-stimulating substance (table 4). These sputums, however, were sanguineous, and since the blood-free sputums of four cases of resolving pneumonia gave negative reactions, it is reasonable to attribute the spasmophilic property to the

presence of free blood, which on clotting, as shown by Clark and Gross, liberates a substance that is readily soluble in alcohol and can induce constriction of smooth muscle. As no grossly demonstrable blood was present in the characteristic sputums of the asthmatic patients, their spasmophilic property need not be attributed to the presence of free blood. The exact nature of the asthmatic, spasmophilic substance was not investigated further on account of the small amount of sputum

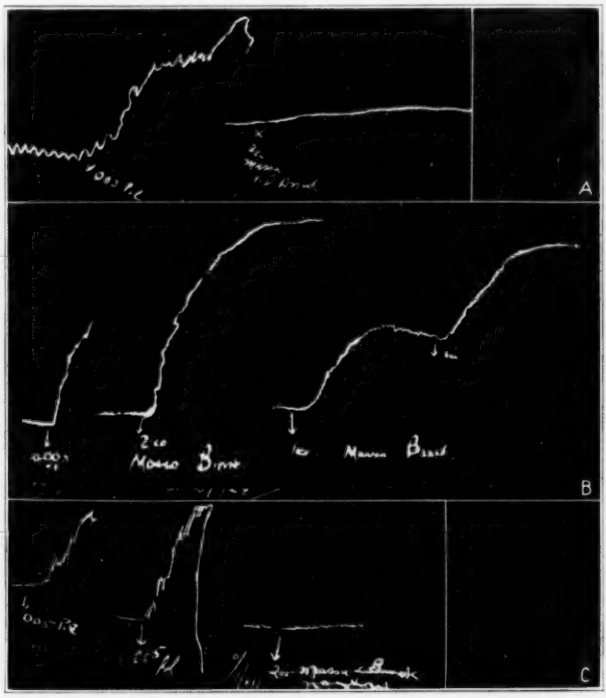

Fig. 1.—v. D. B. was sensitive to oat that had been infested by mites. A skin test done by the intradermal method evoked a severe asthmatic attack, so that it was possible to study this patient's sputum before, during and after the attacks. The results of this study showed a flat curve of the muscle before (*A*), a violent spasm and contraction during (*B*), and again a negative curve after the attack had subsided (*C*).

available. Some of the allergic patients had little or no sputum during attacks.

Figures 1 and 2 have been selected to illustrate typical reactions under various conditions.

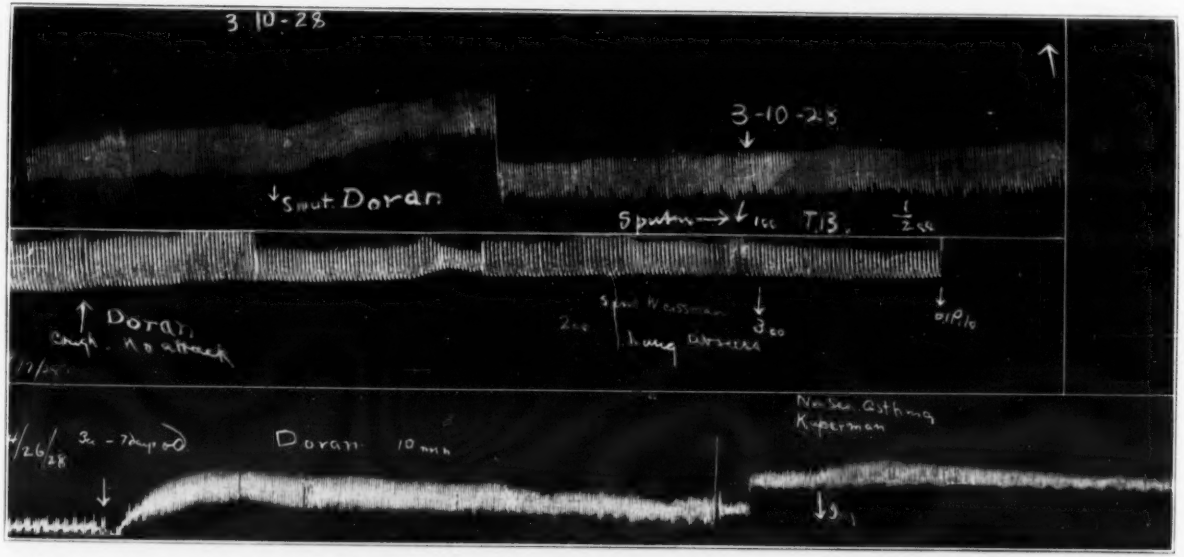

Fig. 2.—D. was sensitive to horse dander, dog hair, timothy and sheep wool. The first asthmatic attack that was investigated occurred on March 10, 1928. The extract of sputum at this time produced a definite contraction of the rabbits' intestine. On April 7, the patient was free from attacks, and the sputum presented no demonstrable spasmophilic substance. On the same strip of muscle, sputum from a case of abscess of the lung and one of pulmonary tuberculosis also gave negative reactions. On April 26, the patient developed another attack. The sputum that was obtained was introduced into the water bath, and the drum was allowed to run ten minutes. The picture presents a progressively increasing contraction of the intestinal strip, both the amplitude and the height of contraction gradually subsiding at the end of the period. On the same strip, a case of nonsensitive asthma was tested and a flat curve is evident.

SUMMARY AND CONCLUSIONS

The sputum of sensitive, asthmatic patients contained an alcohol-soluble substance which is capable of stimulating the contraction of smooth muscle. This substance was absent from the sputum of non-sensitive, asthmatic subjects and of those without asthma. The rusty sputum of patients with lobar pneumonia and with bronchopneumonia gave a positive reaction, but the effect may be attributed to the presence of blood, as blood-free sputum from patients with resolving pneumonia gave no reactions. The exact nature of the spasm-producing substance in the sputum was not elucidated.

CORRECTION

In an article by M. M. Wintrobe on "Blood of Normal Young Women Residing in a Subtropical Climate," which appeared in the February issue, an error occurred in the heading for table 4 on page 300. This should read "Observations on the Blood of Healthy Young Women from 17 to 30 Years of Age in Different Parts of the World."